(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2013 (17.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/008218 Al

(51) International Patent Classification:
A61K 31/357 (2006.01) *A61K 9/20* (2006.01)
A61K 31/496 (2006.01) *A61P 33/06* (2006.01)

(21) International Application Number:
PCT/IB20 12/0536 14

(22) International Filing Date:
13 July 2012 (13.07.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
13/183,1 19 14 July 201 1 (14.07.201 1) US
2703/DEL/201 1 19 September 201 1 (19.09.201 1) IN
2156/DEL/2012 12 July 2012 (12.07.2012) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/008218 A1

(54) Title: STABLE DOSAGE FORMS OF ARTEROLANE AND PIPERAQUINE

(57) Abstract: The field of the invention relates to stable oral dosage forms comprising, (a) cis-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl) amino]carbonyl]-methyl]-l',2',4'-trioxaspiro[4.5]decane hydrogen maleate (Active compound I); (b) piperaquine; and (c) one or more pharmaceutically acceptable excipients; and processes for their preparation, especially wherein the dosage form is prepared by a dry process.

STABLE DOSAGE FORMS OF ARTEROLANE AND PIPERAQUINE

Field of the Invention

The field of the invention relates to stable oral dosage forms comprising spiro or dispiro 1,2,4-trioxolane antimalarials, or their pharmaceutically acceptable salts, prodrugs and analogues and processes for their preparation.

Background of the Invention

Malaria, the most common parasitic disease of humans, remains a major health and economic burden in most tropical countries. Large areas of Central and South America, Hispaniola (Haiti and the Dominican Republic), Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania are considered as malaria-risk areas. It leads to a heavy toll of illness and death, especially amongst children and pregnant women. According to the World Health Organization, it is estimated that the disease infects about 400 million people each year, and around two to three million people die from malaria every year. There are four kinds of malaria parasites that infect human: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae.

Malaria spreads from one person to another by the bite of mosquito, Anopheles gambiae, which serves as vector. When a mosquito sucks the blood of human, sporozoites are transfused into the human body together with saliva of the mosquito. The sporozoites enter into the hepatocytes, reproduce asexually and finally enter into the blood stream. The parasites continue to multiply inside the red blood cells, until they burst and release large number of merozoites. This process continues, destroying a significant number of blood cells and causing the characteristic paroxysm ("chills and fever") associated with the disease. In the red blood cells, some of the merozoites become male or female gametocytes. These gametocytes are ingested by the mosquito when it feeds on blood. The gametocytes fuse in the vector's gut; sporozoites are produced and are migrated to the vector's salivary glands.

The clinical symptoms of malaria are generally associated with the bursting of red blood cells causing an intense fever associated with chills that can leave the infected individual exhausted and bedridden. More severe symptoms associated with repeat

infections and/or infection by Plasmodium falciparum include anaemia, severe headaches, convulsions, delirium and, in some instances, death.

Quinine, an antimalarial compound that is extracted from the bark of cinchona tree, is one of the oldest and most effective drugs in existence. Chloroquine and mefloquine are the synthetic analogs of quinine developed in 1940's, which due to their effectiveness, ease of manufacture, and general lack of side effects, became the drugs of choice. The downside to quinine and its derivatives is that they are short-acting and have bitter taste. Further, they fail to prevent disease relapses and are also associated with side effects commonly known as "Chinchonism syndrome" characterized by nausea, vomiting, dizziness, vertigo and deafness. However, in recent years, with the emergence of drug-resistant strains of parasite and insecticide-resistant strains of vector, the treatment and/or control of malaria is becoming difficult with these conventional drugs.

Malarial treatment further progressed with the discovery of Artemisinin (qinghaosu), a naturally occurring endoperoxide sesquiterpene lactone isolated from the plant Artemisia annua (Meshnick et al., Microbiol. Rev. 1996, 60, p. 301-315; Vroman et al., Curr. Pharm. Design, 1999, 5, p. 101-138; Dhingra et al., 2000, 66, p. 279-300), and a number of its precursors, metabolites and semi-synthetic derivatives which have shown to possess antimalarial properties. The antimalarial action of artemisinin is due to its reaction with iron in free heme molecules of the malaria parasite, with the generation of free radicals leading to cellular destruction. This initiated a substantial effort to elucidate its molecular mechanism of action (Jefford, dv. Drug Res. 1997, 29, p. 271-325; Cumming et al., Adv. Pharmacol. 1997, 37, p. 254-297) and to identify novel antimalarial peroxides (Dong and Vennerstrom, Expert Opin. Ther. Patents 2001, 11, p. 1753-1760).

Although the clinically useful artemisinin derivatives are rapid acting and potent antimalarial drugs, they have several disadvantages including recrudescence, neurotoxicity, (Wesche et al., Antimicrob. Agents. Chemother. 1994, 38, p. 1813-1819) and metabolic instability (White, Trans. R. Soc. Trop. Med. Hyg., 1994, 88, p. 41-43). A fair number of these compounds are quite active in vitro, but most suffer from low oral activity (White, Trans. R. Soc. Trop. Med. Hyg., 1994, 88, p. 41-43 and van Agtmael et al., Trends Pharmacol. Sci., 1999, 20, p. 199-205).

Further all these artemisinin derivatives are conventionally obtained from plant source and are therefore expensive. As the cultivation of the plant material is dependent on many factors including the weather conditions, the supply source thus becomes finite and there are chances of varying yield and potency. This leads to quality inconsistencies and supply constraints. As malaria is more prevalent in developing countries, a switch to cheaper and effective medicine is highly desirable.

Thus there exists a need in the art to identify new peroxide antimalarial agents, especially those which are not dependent on plant source and can be easily synthesized, are devoid of neurotoxicity, and which possess improved solubility, stability and pharmacokinetic properties.

Following that, many synthetic antimalarial 1,2,4-trioxanes (Jefford, Adv. Drug Res. 1997, 29, p. 271-325; Cumming et al., Adv. Pharmacol. 1997, 37, p. 254-297), 1,2,4,5-tetraoxanes (Vennerstrom et al., J. Med. Chem., 2000, 43, p. 2753-2758), and other endoperoxides have been prepared. Various patents/applications disclose means and method for treating malaria using Spiro or dispiro 1,2,4-trioxolanes for example, U.S. Patent Application No. 2004/0186168 and U.S. Patent Nos. 6,486,199 and 6,825,230. The present invention relates to solid dosage forms of the various spiro or dispiro 1,2,4-trioxolanes antimalarial compounds disclosed in these patents/applications and are incorporated herein by reference.

Active compounds representing various Spiro and dispiro 1,2,4-trioxolane derivatives possess excellent potency, efficacy against Plasmodium parasites, and a lower degree of neurotoxicity, in addition to their structural simplicity and ease of synthesis. Furthermore, these compounds have half-lives which are believed to permit short-term treatment regimens comparing favorably to other artemisinin-like drugs. In general, the therapeutic dose of trioxolane derivative may range between about 0.1-1000 mg/kg/day, in particular between about 1-100 mg/kg/day. The foregoing dose may be administered as a single dose or may be divided into multiple doses. For malaria prevention, a typical dosing schedule could be, for example, 2.0-1000 mg/kg weekly beginning 1-2 weeks prior to malaria exposure, continued up to 1-2 weeks post-exposure.

Monotherapy with artemisinin (natural or synthetic) class of drugs might cure the patients within 3 days, however perceiving the potential threat of the malarial parasite

developing resistance towards otherwise very potent artemisinin class of drugs, WHO had strictly called for an immediate halt to the provision of single-drug artemisinin malaria pills. Combination therapy in case of malaria retards the development of resistance, improve efficacy by lowering recrudescence rate, provides synergistic effect, and increase exposure of the parasite to the drugs.

Artemsinin based combinations are available in the market for a long time. Artemether-lumafentrine (Co-artem®) was the first fixed dose antimalarial combination containing an artemisinin derivative and has been known since 1999. This combination has passed extensive safety and efficacy trials and has been approved by more than 70 regulatory agencies. Co-artem® is recommended by WHO as the first line treatment for uncomplicated malaria.

Other artemisinin based combinations include artesunate and amodiaquine (Coarsucam®), and dihydroartemisin and piperaquine (Eurartesim®). Unfortunately, all the available artemisinin based combinations have complicated dosage regimens making it difficult and inconvenient for a patient to comply completely with the total prescribed duration. For example, the dosage regimen of Co-artem® for an adult having body weight of more than 35 kg includes 6 doses over three days. The first dose comprises four tablets initially, the second dose comprises four tablets after eight hours, the third to sixth doses comprise four tablets twice for another two days; making it a total of 24 tablets. The dosage regimen of Coarsucam® for an adult having body weight of more than 36 kg or age above 14 years includes three doses over three days; each dose comprises two tablets; making it a total of six tablets. The dosage regimen of Eurartesim® for an adult having body weight between 36 kg - 75 kg includes 3 doses over three days, each dose comprises of three tablets, making it a total of nine tablets.

It is evident that the available artemisinin-based combinations have a high pill burden on patients as they need to consume too many tablets. As noted above, this may increase the possibility of missing a few doses, and, consequently, could result in reduced efficacy due to non-compliance and may even lead to development of resistance for the drug.

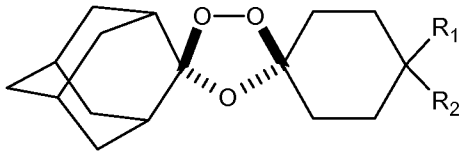
Therefore, there is an urgent and unmet need for anti-malarial combinations with a simplified daily dosing regimen that reduces the pill burden and would increase patient compliance.

Apart from simplifying the regimen, there are certain limitations for formulators developing formulations with trioxolones, the first being their susceptibility to degradation in presence of moisture that results in reduced shelf lives. Another is their bitter taste, which can result in poor compliance of the regimen or selection of another, possibly less effective, therapeutic agent.

We have now discovered that a stable antimalarial oral solid dosage form comprising spiro or dispiro 1,2,4-trioxolanes can be prepared by controlling the water content below a certain critical limit. Further, the bitter taste can be masked by applying a film coating layer to the solid dosage form.

Summary of the Invention

In one general aspect there is provided a stable solid oral dosage form that includes a therapeutically effective amount of a compound having the structural Formula I,



Formula I

and its enantiomers, diastereomers, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates, wherein:

R_1 and R_2 are same or different and are selected from hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that are optionally interrupted by one or more oxygen, sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy group, and a halogen, and further providing that the spirocyclohexyl rings attaching R_1 and R_2 are optionally interrupted by one or more oxygen, sulfur, or nitrogen atoms; and one or more pharmaceutically acceptable excipients, wherein not more than 5% w/w total related

substances are formed on storage at 40°C ± 2°C and 75% ± 5% relative humidity over a period of 6 months.

Embodiments of the solid oral dosage form may include one or more of the following features. For example, the dosage form may include one or more of other antimalarial drugs. The other antimalarial drugs may include quinine, mefloquine, lumefantrine, sulfadoxine-pyrimethamine, dihydroartimisinin, piperaquine, chloroquine, amodiaquine, proguanil, atovaquone, chloroproguanil, dapsone, fosmidomycin, tetracycline, DB 289 (pafuramidine maleate), clindamycin, or their salts and derivatives thereof. In particular, piperaquine, lumefantrine and DB 289 may be used.

In another general aspect, there is provided a method of treatment of malaria. The method includes administering a solid dosage form that includes a therapeutically effective amount of a compound of structural Formula I; and one or more pharmaceutically acceptable excipients, wherein not more than 5% w/w total related substances are formed on storage at 40°C ± 2°C and 75% ± 5% relative humidity over a period of 6 months.

In another aspect, there is provided a method of treatment of malaria, wherein the method includes administering a solid dosage form that includes a therapeutically effective amount of a compound of structural Formula I, formulated using a dry or non-aqueous process.

In another aspect, there is provided a stable solid oral dosage form, wherein the dosage form includes a therapeutically effective amount of a compound of structural Formula I; at least one other antimalarial drug selected from lumefantrine, piperaquine, or DB 289; and one or more pharmaceutically acceptable excipients.

Embodiments of the oral dosage form may include one or more of the following features. For example, the water content of the dosage form may not be more than 6.5% w/w.

In another general aspect, there is provided a stable oral solid dosage form comprising cis-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl) amino]carbonyl]-methyl]-r,2',4'-trioxaspiro[4.5]decane hydrogen maleate; piperaquine; and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) cis-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino]carbonyl]-methyl]-r,2',4'-trioxaspiro[4.5]decane hydrogen maleate (Active compound I);

(b) piperaquine; and

(c) one or more pharmaceutically acceptable excipients

wherein the dosage form is prepared by a dry process.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) Active compound I; and

(b) piperaquine

wherein the total drug content is within the range of from about 25% to about 85% w/w based on the total weight of the dosage form.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) Active compound I in an amount of from about 5% to about 25%; and

(b) piperaquine in an amount of from about 40% to about 80%, w/w based on the total weight of the dosage form.

In another general aspect, there is provided a stable solid oral dosage comprising;

(a) Active compound I in an amount of from about 5% to about 25%; and

(b) piperaquine in an amount of from about 40% to about 80%

wherein the total drug content does not exceed 85% w/w based on the total weight of the dosage form.

In another general aspect, there is provided a stable solid oral dosage of Active compound I and piperaquine; wherein the dosage form has dissolution performance such that more than 70% w/w of the Active compound I dissolves within 45 minutes, in a pH 4.5 acetate buffer with 2% tween 80, in USP type II apparatus.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) Active compound I and

(b) piperaquine; in a weight ratio of about 1:1 to about 1:10.

In another general aspect, there is provided a stable oral solid dosage form comprising Active compound I present in a dose range of about 100 to about 300 mg and piperaquine present in a dose range of about 700 mg to about 850 mg.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) Active compound I in an amount of from about 5% to about 25%;

(b) piperaquine in an amount of from about 40% to about 80%;

(c) diluent in an amount of from about 10% to about 40%;

(d) disintegrant in an amount of from about 1% to about 10%; and

(e) lubricant in an amount of from about 1% to about 5%; w/w based on the total weight of the dosage form.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) Active compound I;

(b) piperaquine;

(c) microcrystalline cellulose;

(d) crospovidone; and

(e) magnesium stearate.

In another general aspect there is provided a stable oral solid dosage comprising;

(a) Active compound I in an amount of from about 5% to about 25%;

(b) piperaquine in an amount of from about 40% to about 80%; and

(c) microcrystalline cellulose in an amount of from about 10% to about 40%; w/w based on the total weight of the dosage form.

In another general aspect, there is provided a stable solid oral dosage form comprising Active compound I and microcrystalline cellulose in a weight ratio of about 1:1 to about 1:5.

The pharmaceutically acceptable excipients may be selected from the group consisting of binders, diluents, glidants/lubricants, disintegrants, surfactants and coloring agents.

The solid dosage form may be in the form of a tablet, capsule, pellet, pill, granule or powder. Particularly the dosage form is a tablet or a capsule. More particularly, the dosage form is a tablet.

In another general aspect, there is provided a stable solid oral dosage form, wherein the dosage form is processed and stored at a temperature below 27°C and relative humidity 50%.

Embodiments of the process may include one or more of the following features. For example, the dosage form is formulated using a dry or non-aqueous process. The non-aqueous process may include a non-aqueous granulating liquid selected from ethanol, isopropyl alcohol, acetone, or dichloromethane for preparing the binder solution. The dry process may include direct compression or dry granulation. Dry granulation may be compaction or slugging. In particular, the dry granulation may be compaction for example, dry roller compaction.

In another general aspect, there is provided a process for the preparation of a stable solid oral dosage form, comprising the steps of;

(a) blending Active compound I, piperaquine, and one or more intragranular excipients;

(b) milling, grinding or sieving the blend by roller compaction to form granules;

(c) blending the granules with one or more extragranular excipients;

(d) compressing the blend into tablets or filling into capsules.

In another general aspect, there is provided a process for the preparation of a stable solid oral dosage form, comprising the steps of;

(a) blending Active compound I, piperaquine, and one or more intragranular excipients;

(b) granulating the blend by slugging;

(c) blending the granules with one or more extragranular excipients;

(d) compressing the blend into tablets or filling into capsules.

In another general aspect, there is provided a process for the preparation of a stable solid oral dosage form, comprising the steps of;

(a) blending Active compound I, piperaquine, and one or more pharmaceutically acceptable excipients; and

(b) directly compressing the blend into tablets or filling into capsules.

In another general aspect, there is provided a process for the preparation of a stable solid oral dosage form, comprising the steps of;

(a) granulating a blend of one or more excipients;

(b) drying the excipient granules;

(c) blending excipient granules with Active compound I and piperaquine; and

(d) compressing the blend into tablets or filling into capsules.

The tablet may be coated with layer(s) of one or more film forming polymers.

In another general aspect, there is provided a method of treatment of malaria. The method includes administering a stable oral solid dosage form comprising;

(a) Active compound I;

(b) piperaquine; and

(c) one or more pharmaceutically acceptable excipients

wherein the dosage form is prepared by a dry process.

In another general aspect, there is provided a stable solid oral dosage form comprising;

(a) 150 mg of Active compound I and

(b) 750 mg of piperaquine

wherein the dosage form is administered once a day for three days.

In another general aspect, there is provided a method of treating malaria comprising administering a stable solid oral dosage form comprising;

(a) 150 mg Active compound I and

(b) 750 mg of piperaquine

wherein the dosage form is administered once a day for three days.

The details of one or more embodiments are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

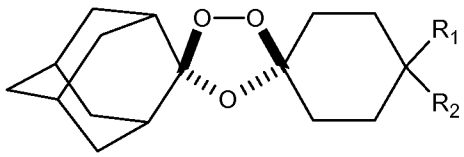
Detailed Description of the Invention

We have now discovered that stable solid oral dosage forms of Spiro or dispiro 1,2,4-trioxolane antimalarials can be prepared which do not degrade significantly and provide acceptable shelf life.

The term "stable" as used herein refers to chemical stability of active compound in solid dosage forms against decomposition occurring during shelf life due to hydrolysis, wherein not more than 5% w/w total related substances are formed on storage at 40°C ± 2°C and 75% ± 5% relative humidity over a period of 6 months.

The present invention provides stable solid oral dosage forms of the active compound, by using excipients having low water content and manufactured using dry or non-aqueous formulation processes.

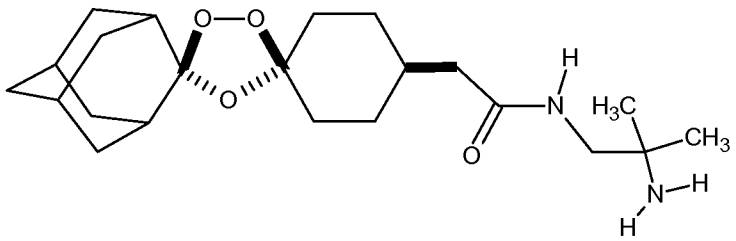
The term "active compound" as used herein includes spiro or dispiro 1,2,4-trioxolane compound of structural Formula I



Formula I

wherein R_1 and R_2 are same or different and are selected from hydrogen, substituted or unsubstituted linear or branched alkyl, aryl, and alkaryl groups and substituted or unsubstituted alicyclic groups that are optionally interrupted by one or more oxygen,

sulfur or nitrogen atoms, substituted or unsubstituted aromatic or heterocyclic groups that may be interrupted by one or more oxygen, sulfur or nitrogen atoms, a hydroxy group, and a halogen, and further providing that the spirocyclohexyl rings attaching R_1 and R_2 are optionally interrupted by one or more oxygen, sulfur, or nitrogen atoms. In particular, it includes compounds of Formula I, wherein R_1 is hydrogen, for example, compounds of structural Formula II.



Formula II

Active compound includes one or more of the various spiro and dispiro trioxolane derivatives disclosed in U.S. Application No. 2004/0 186168 and U.S. Patent Nos. 6,486,199 and 6,825,230, which are incorporated herein by reference. These trioxolanes are relatively sterically hindered on at least one side of the trioxolane heterocycle which provides better in vivo activity, especially with respect to oral administration. Particularly, spiro and dispiro 1,2,4-trioxolanes derivatives possess excellent potency and efficacy against Plasmodium parasites, and a lower degree of neurotoxicity.

The term "Active compound I" herein means cis-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino]carbonyl]-methyl]- 1',2',4'-trioxaspiro[4.5]decane hydrogen maleate. The Active compound I may be present in an amount of from about 5% to about 25%, w/w based on the total dosage form.

Further, perceiving the potential threat of the malarial parasite developing resistance towards otherwise very potent artemisinin class of drugs, WHO has called for an immediate halt to the provision of single-drug artemisinin malaria pills. In the case of malaria, combination therapy has been applied since around 1990. However, this strategy is being hampered because the Plasmodium parasite has developed resistance, as a result of monotherapy, to certain components of currently applied combination drugs. Combination therapy is expected to retard the development of resistance, improve efficacy

by lowering recrudescence rate, provide synergistic effect, and increase exposure of the parasite to the drugs.

Embodiments of the solid oral dosage of the present invention further include one or more of antimalarial drugs. The antimalarial drugs may include quinine, mefloquine, lumefantrine, sulfadoxine-pyrimethamine, dihydroartimisinin, piperaquine, chloroquine, amodiaquine, proguanil, atovaquone, chloroproguanil, dapsone, fosmidomycin, tetracycline, DB 289 (pafuramidine maleate), clindamycin, or their salts and derivatives thereof. In particular, piperaquine, lumefantrine and DB 289 may be used; however piperaquine remains the preferred one.

Selection of combination as an antimalarial therapy is based on certain attributes. Synthetic artemisinin derivatives exhibit their action by their reaction with the iron in free heme molecules in the malaria parasite with the generation of free radicals leading to cellular destruction. On the other hand bisquinoline derivatives such as piperaquine interfere with the detoxification of haemin in the digestive vacuole of the parasite to non-toxic malaria pigment, so that haemin can generate free radicals and membrane damage follows. The unrelated mode of action of the two drugs would provide improved therapy, and treatment against all stages of parasites including gametocytes. Additionally, since synthetic artemisinin derivatives are very efficacious and highly potent, these would thereby treat the symptoms quickly, exhibiting fast recovery rates. The combination of synthetic artemisinin derivatives and bisquinoline derivatives such as piperaquine provide a short duration of treatment.

Piperaquine is a bisquinoline compound that has antimalarial activity against both *P. vivax* and *P. falciparum,* including strains of chloroquine resistant *P. falciparum.* The tolerability, efficacy, pharmacokinetic profile, low cost and longer-acting piperaquine makes it a very perfect candidate for use in combination with short and rapidly acting Active compound I. Piperaquine of the present invention includes piperaquine phosphate. Piperaquine may be present in an amount of from about 40% to about 80%, w/w based on the total dosage form.

The total drug content of the oral dosage forms of the present invention is within the range of about 25% to about 85%, and in particular does not exceed 85% w/w based on the total dosage form.

The oral dosage forms of the present invention comprise Active compound I and piperaquine in a weight ratio of about 1:1 to about 1:10.

The oral dosage forms of the present invention comprise Active compound I present in a dose range of about 100 mg to about 300 mg and piperaquine present in a dose range of about 700 mg to about 850 mg.

The oral dosage forms of the present invention comprise Active compound I present in a unit dose of 100 mg, 150 mg or 250 mg and piperaquine present in a unit dose of750 mg.

The oral dosage forms of the present invention comprise Active compound I in a unit dose of about 100 mg and piperaquine present in a unit dose of about 750 mg.

The oral dosage forms of the present invention comprise Active compound I in a unit dose of about 150 mg and piperaquine present in a unit dose of about 750 mg

The oral dosage forms of the present invention comprise Active compound I in a unit dose of about 200 mg and piperaquine present in a unit dose of about 750 mg

The dosage regimen of the present invention includes administering a fixed dose combination of 150 mg Active compound I and 750 mg of piperaquine once a day for three days.

The dose of Active compound I herein means dose equivalent to Active compound I free base.

The dosage regimen of the present invention includes three doses over three days. The first dose is administered immediately on diagnosis, the second dose about 24 hours after the first dose, and the third dose about 24 hours after the second dose.

The dosage regimen of the present invention is suitable for all patients aged from 12 to 65 years and thus eliminates the need for calculating dose based on individual weight parameters. In the existing artemisinin based combinations, the dose is calculated with respect to the individual weight of the patient and in many cases the tablets are scored to adjust the dose. However, the dosage regimen of this combination is surprisingly simple and effective both for patients and for prescribers.

Solid dosage form as used herein is selected from a group consisting of tablets or coated tablets, capsules, pellets, pills, granules and powders. A particularly suitable solid dosage form is that of tablets.

Further, it has been observed through exhaustive experimentation that when the active compound is formulated into dosage forms, including liquid as well as solid dosage forms, it gets degraded by hydrolysis. The degradation may be due to water associated with the excipients or added during the course of processing. Thus, liquid oral dosages forms such as aqueous syrups, suspensions or solutions having desired shelf life could not be successfully prepared. Further, preparation of solid oral dosage forms of active compound using techniques involving use of water such as wet granulation, spray drying, or extrusion-spheronization processes resulted in dosage forms with wavering stability results. However, acceptable stability results were obtained when the solid dosage forms were formulated using appropriate excipients with low water content and a process in which water was absent, such as dry granulation, direct compression or non-aqueous granulation. In case where excipients were granulated using water, the excipient granules were dried appropriately before blending with the active compound as such or with active compound containing granules, and processed into solid dosage forms of acceptable stability.

The role of excipients and water content was evaluated by conducting compatibility studies of the active compound with various excipients in different proportions, and evaluating the extent of degradation by forced degradation at 60°C over the period of 2 weeks and at 50°C for 4 weeks. The water content was analyzed using Karl Fischer method and the total related substances (% w/w) were determined by HPLC method. The results of the study are represented below in Table 1.

Table 1: Compatibility studies of active compound (Active compound I) with various excipients

Excipient	Drug: Excipient	Water (%w/w)	Total Related Substance (Percent w/w)		
			Initial	After 4 weeks/ 50°C	After 2 weeks/ 60°C
Croscarmellose sodium	1:0.5	0.59	0.09	0.34	0.35
Cross povidone	1:0.5	3.49	0.13	0.40	0.68
Sodium starch glycolate	1:0.5	1.43	0.13	0.43	0.89
Hydroxypropyl methylcellulose 5cps	1:0.5	1.22	0.17	0.70	1.05
Polyvinyl pyrrolidone K 30	1:0.5	3.02	0.00	0.33	0.79
Sodium lauryl sodium	1:0.5	0.79	0.15	0.92	1.59
Opadry®	1:0.5	0.46	0.17	1.85	0.96
Titanium dioxide	1:0.5	0.18	0.16	0.57	0.93
Talc	1:0.1	0.12	0.15	0.63	0.90
Mg. Stearate	1:0.1	0.46	0.13	0.65	0.86
Aerosol	1:0.1	0.27	0.14	0.66	0.86
Polyethylene glycol 400	1:0.1	0.88	0.14	0.66	0.68
Microcrystalline cellulose	1:2	3.69	0.19	0.70	0.74
Starch	1:2	4.73	0.08	0.60	0.74
Dicalcium phosphate	1:2	2.01	0.07	0.77	1.32
Pearlitol	1:2	0.02	0.14	0.72	0.77
Micro crystalline cellulose	1:10	4.94	0.39	0.78	1.02
Starch	1:10	-	0.07	0.60	4.13
Dicalcium phosphate	1:10	2.14	0.17	0.61	6.07
Pearlitol	1:10	0.52	0.14	0.46	0.70

The study clearly indicates the importance of use of excipients having low water or moisture content in stabilizing solid dosage forms of the active compound. In the present invention, we have discovered that the use of excipients having water content less than 6.5% w/w surprisingly increases the stability of the active compound, and thus provides reasonably long shelf lives. Starch was found to be incompatible with the active compound when used in higher amounts. Further, lactose was also found to be incompatible due to degradation by other mechanisms such as Maillard reaction, and dicalcium phosphate was not preferred due to an increase in related substances at 60°C.

Micro-crystalline cellulose, however, gave the most satisfactory results.

The stable solid oral dosage forms of the present invention may further comprise one or more pharmaceutically acceptable excipients, which include all physiologically inert excipients used in the art for the preparation of solid dosage forms. Examples include binders, diluents, glidants/lubricants, disintegrants, surfactants, coloring agents, and the like. The excipients may be used either intragranularly or extragranularly, or both. The weight ratio of active compound and excipients in the dosage forms may vary from about 1.5:1 to about 1:30.

Examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, agar, tragacanth and sodium alginate, or mixtures thereof.

Examples of diluents include cellulose powdered, microcrystalline cellulose, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, mannitol, sorbitol, sucrose, sugar compressible, and sugar confectioners, in particular microcrystalline cellulose. The diluents may be present in an amount from about 10% to about 40% w/w based on the total weight of the dosage form. Further the weight ratio of Active compound I to microcrystalline cellulose may vary from about 1:1 to about 1:5.

Examples of disintegrants include clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose and soy polysaccharides, in particular crospovidone. The disintegrant may be present in an amount from about 1% to about 10% w/w based on the total weight of the dosage form.

Examples of lubricants or glidants include talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, microcrystalline cellulose, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, in particular magnesium stearate. The lubricant may be present in an amount from about 1% to about 5%, w/w based on the total weight of the dosage form.

Examples of surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in sweetener compositions. These include polyethoxylated fatty acids and its derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol-20 dioleate, polyethylene glycol 4-150 mono dilaurate, polyethylene glycol—20 glyceryl stearate; alcohol—oil transesterification products, for example polyethylene glycol-6 corn oil; polyglycerized fatty acids, for example polyglyceryl—6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides, for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol—20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol—20 cetyl ether, polyethylene glycol- 10-100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene-polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

The coloring agents include any FDA approved colors for oral use.

The solid dosage forms may further be coated with one or more functional and/or non-functional layers comprising film-forming polymers, and other coating additives.

Examples of film-forming polymers include cellulose derivatives such as ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, partially hydrolyzed polyvinyl alcohol, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes such as polyethylene glycol; and methacrylic acid polymers such as Eudragit® RL and RS. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry®, may also be used for coating.

The coating additives comprise one or more of plasticizers, glidants or flow regulators, opacifiers and lubricants.

The pharmaceutical acceptable excipients and/or film forming polymers and coating additives may be selected to provide an immediate-release profile or a modified release profile.

Solid dosage forms of Active compound I may be prepared by densifying Active compound I and one or more excipients, and processing into solid dosage forms. Densification may be carried out using any conventional method known in the art. In particular, granulation or extrusion-spheronization may be used.

In one of the embodiments, stable oral tablets of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of a diluent, lubricant, and disintegrant; passing the blend through a roller compactor to form a compact mass; reducing the compact mass into granules of suitable size; blending the granules with extragranular portion of a lubricant, disintegrant, and diluent in a double cone blender; and finally compressing into tablets using suitable tooling.

In another embodiment, stable oral tablets of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of a diluent, lubricant, and disintegrant; compressing the blend in a heavy tabletting press to form slugs; reducing the slugs into granules of suitable size; blending the granules with extragranular portion of a lubricant, disintegrant, and diluent in a double cone blender; and finally compressing into tablets using suitable tooling.

In another embodiment, stable oral capsules of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of a diluent, lubricant, and disintegrant; passing the blend through a roller compactor to form a compact mass; reducing the compact into granules of a suitable size; blending the granules with extragranular portion of a lubricant in a double cone blender; and finally filling into capsules of a suitable size.

In another embodiment, stable oral capsules of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of a diluent, lubricant, and disintegrant; compressing the blend in a heavy tabletting press to form slugs; reducing the slugs into granules of a suitable size; blending the granules with extragranular portion of lubricant in a double cone blender; and finally filling into capsules of a suitable size.

In another embodiment, stable oral tablets of Active compound I may be prepared by a process comprising the steps of blending Active compound I, a diluent, a lubricant and a disintegrant; and directly compressing into tablets using suitable tooling.

In another embodiment, stable oral capsules of Active compound I may be prepared by a process comprising the steps of blending Active compound I, a diluent, and a lubricant; and filling into capsules of a suitable size.

In another embodiment, stable oral tablets of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of a diluent, and disintegrant; wet granulating the blend with a non aqueous granulating fluid or a solution/dispersion of pharmaceutically acceptable excipients in the non-aqueous granulating fluid; drying and reducing the granules to a suitable size, blending the granules with extragranular portion of a lubricant, disintegrant and diluent in a double cone blender; and finally compressing into tablets using suitable tooling.

In yet another embodiment, stable oral capsules of Active compound I may be prepared by a process comprising the steps of blending Active compound I and intragranular portion of diluent, and disintegrant; wet granulating the blend with a non aqueous granulating fluid or a solution/dispersion of pharmaceutically acceptable excipients in the non-aqueous granulating fluid; drying and reducing the granules to a suitable size; blending the granules with extragranular portion of lubricant in a double cone blender; and finally filling into capsules of a suitable size.

Examples of non-aqueous granulating fluid include organic solvents such as methanol, ethanol, isopropyl alcohol, dichloromethane, acetone, or mixtures thereof.

In yet another embodiment, tablets prepared by any of the above described processes may further be coated with film-forming polymers and one or more coating additives, using techniques well known in the art such as spray coating in a conventional coating pan or a fluidized bed processor or dip coating. Alternatively, coating can also be performed using a hot melt technique.

The coating layers over the tablet may be applied as a solution/dispersion of coating components in a suitable solvent. Examples of solvents used for preparing a solution/dispersion of the coating ingredients include methyl alcohol, ethyl alcohol,

isopropyl alcohol, n-butyl alcohol, acetone, acetonitrile, chloroform, methylene chloride, water and the like, and mixtures thereof.

In still another embodiment, one or more of another antimalarial drug selected from piperaquine, lumefantrine, and DB 289 (pafuramidine maleate) may be added in the blend comprising active compound, in any of the embodiments above.

The dosage form of the present invention is processed and stored at a temperature below 27°C and relative humidity 50%.

The invention described herein is further illustrated by the following examples, which should not be construed as limiting the scope of the invention.

EXAMPLES

Example 1:

Ingredients	**Percent w/w**
Intragranular	
Maleate salt of a compound of Formula II (active compound) [Active compound I]	43.2
Microcrystalline Cellulose	46.67
Magnesium stearate	0.75
Extragranular	
Microcrystalline Cellulose	5.63
Croscarmellose sodium	3.0
Magnesium stearate	0.75
Total Percentage	100%
Coating	
Opadry® OY SS 58910 white	2.5
Water	q.s
Total weight	***615***
Water content	***<6.55% w/w***

Procedure:

1. Active compound I and intragranular portion of microcrystalline cellulose were sieved through sieve BSS #44 and mixed together in a double cone blender to form a uniform blend.

2. To the blend of step 1, intragranular portion of sifted magnesium stearate was added and blended for about 5 minutes.

3. The blend of step 2 was compacted in a roller compactor and was sifted through sieve BSS #22 to form granules.

4. Extragranular portion of microcrystalline cellulose, croscarmellose sodium and magnesium stearate were sieved through sieve BSS # 44 and blended with the granules of step 3.

5. The blend of step 4 was compressed using suitable size punches to obtain compressed tablets.

6. The tablets as obtained from step 5 were coated with Opadry® using conventional coating techniques.

The tablets prepared as per Example 1 were subjected to stability studies at 25°C/ RH 60%, 30°C/RH 65% and 40°C/RH 75% over a period of 6 months. The results are summarized in Table 2. The results of *in vitro* drug release analyzed at predetermined time periods are given in Table 3.

Table 2: Total related substances* (Percent w/w)

Storage Condition	Initial	1 month	2 months	3 months	6 months
25ºC and 60% relative humidity	0.11	-	-	0.27	0.28
30ºC and 65% relative humidity	0.11	0.37	0.27	0.29	0.34
40ºC and 75% relative humidity	0.11	0.55	0.67	1.40	1.82

* % Total Related Substance should not be more than 5% w/w.

Table 3: Percentage (%) of *In vitro* drug release in USP II apparatus* (media: 2% tween 80 in water, 900ml 75 rpm, in 45 min)

Storage Condition	Initial	1 month	2 months	3 months	6 months
25ºC and 60% relative humidity	93	-	-	101	95
30ºC and 65% relative humidity	93	98	93	94	96
Temperature 40ºC and 75% relative humidity	93	98	96	92	94

*The in vitro drug release (%w/w) should not be less than 70% (Q) of the labeled amount dissolved in 45 minutes.

As evident from the above studies, the tablets prepared by the process of the present invention in which water is absent shows acceptable shelf stability.

Example 2:

Ingredients	**Percent w/w**
Maleate salt of a compound of Formula II (active compound) [Active compound I]	44.33
Microcrystalline Cellulose	51.17
Magnesium stearate	1.5
Croscarmellose sodium	3.0
Total weight	***600 mg***
Water content	***<6.5%***

Procedure:

1. Active compound I, microcrystalline cellulose, croscarmellose sodium and magnesium stearate were sifted through sieve BSS #44.

2. Sifted Active compound I, microcrystalline cellulose, and croscarmellose sodium were mixed in a double cone blender for about 15 minutes to form a uniform blend.

3. To the blend of step 2, sifted magnesium stearate was added and mixed for about 5 minutes.

4. The blend obtained in step 3 was directly compressed using suitable size capsule shape punches to obtain compressed tablets.

Examples 3 and 4:

Ingredients	Example 3 Percent w/w	Example 4 Percent w/w
Intragranular		
Maleate salt of a compound of Formula II (active compound) [Active compound I]	7.68	13.80
Piperaquine phosphate	61.80	55.50
Microcrystalline Cellulose	20.39	21.15
Magnesium stearate	0.44	0.39
Crospovidone	2.21	1.99
Extragranular		
Microcrystalline Cellulose	4.32	3.99
Crospovidone	2.11	1.99
Magnesium stearate	1.05	1.19
Total percentage	100%	100%
Coating		
Opadry® O2B53782 orange	2.5	2.5
Water	q.s	q.s
Total weight (mg)	***1332.5***	***738***
Water content	***<6.55% w/w***	***<6.55% w/w***

Procedure:

1. Active compound I, piperaquine phosphate and intragranular portion of microcrystallme cellulose and crospovidone were sieved through sieve BSS # 44 and mixed together in a double cone blender to form a uniform blend.

2. To the blend of step 1, intragranular portion of sifted magnesium stearate was added and blended for about 5 minutes.

3. The blend of step 2 was compacted in a roller compactor and was sifted through sieve BSS # 18 to form granules.

4. Extragranular portion of microcrystallme cellulose and crospovidone were sieved through sieve BSS # 44 and blended with the granules of step 3.

5. Extragranular portion of magnesium stearate was sieved through sieve BSS # 44 and blended with the blend of step 4 in a double cone blender for about 5 minutes.

6. The blend of step 5 was compressed using suitable size punches to obtain compressed tablets.

7. The tablets as obtained from step 6 were coated with Opadry® using conventional coating techniques and weight built of up to 2.5% w/w.

The tablets prepared as per the Example 3 & 4 were subjected to stability studies at 40°C/RH 75% over a period of 3 months, as represented in Table 4.

Table 4: Percent total related substances* (%w/w)

Ingredient		Initial	1 month	2 months	3 months
Maleate salt of a compound of Formula II [Active compound I]	Example 3	0.19	0.27	0.44	0.54
	Example 4	0.25	0.32	0.45	0.54
Piperaquine phosphate	Example 3	1.16	1.1	1.11	1.16
	Example 4	1.15	1.03	1.13	1.16

* % Total related substance should not be more than 5% w/w.

Example 5:

Ingredients	Percent w/w
Intragranular	
Active compound I	14.60
Piperaquine phosphate	56.30
Microcrystalline Cellulose	16.70
Magnesium stearate	0.43
Crospovidone	2.15
Extragranular	
Microcrystalline Cellulose	4.30
Crospovidone	2.15
Magnesium stearate	0.97
Coating	
Opadry® 02B53782 orange	2.40
Water	q.s
Total weight (mg)	***1332.0***
Water content	***<6.55% w/w***

Procedure:

1. Active compound I, piperaquine phosphate and intragranular portion of microcrystalline cellulose and crospovidone were sieved through sieve BSS # 44 and mixed together.

2. To the blend of step 1, intragranular portion of sifted magnesium stearate was added and blended for about 5 minutes.

3. The blend of step 2 was compacted and compacts were sifted through sieve BSS # 18 to form granules.

4. Extragranular portion of microcrystalline cellulose and crospovidone were sieved through sieve BSS # 44 and blended with the granules of step 3.

5. Extragranular portion of magnesium stearate were sieved through sieve BSS # 44 and blended with the blend of step 4 in a double cone blender for about 5 minutes.

6. The blend of step 5 was compressed using suitable size punches to obtain compressed tablets.

7. The tablets as obtained from step 6 were coated with Opadry® using conventional coating techniques and weight built of up to 2.4%w/w.

Table 5: Percentage (% w/w) of *In vitro* drug release of Active compound I, from example 5, in USP II apparatus* (media: 2% tween 80 in water, 900ml, 75 rpm)

Time (minutes)	(Percent w/w)
15	88
30	87
45	90

*The in vitro drug release (% w/w) should not be less than 70% (Q) of the labeled amount dissolved in 45 minutes.

A Phase II, double blind, parallel group, randomized, dose finding study was performed to determine the safety and efficacy of three dose levels (50 mg, 100 mg and 200 mg) of Active compound I administered for three days in patients with uncomplicated P. falciparum malaria. Preliminary data showed that the mean parasite clearance time for the patient on 50 mg was 52 hours, and all the 3 patients who were followed up for 28

days showed reappearance of parasites. Patients receiving 100 mg had a parasite clearance time of 46.6 hours and 5 of total 6 patients showed reappearance of parasites. Patients receiving 200 mg had a parasite clearance time of 30.4 hours and 4 out of 5 patients showed adequate clinical and parasitological response (ACPR) at day 28. Only 1 patient showed reappearance of parasites. The results obtained so far indicate that Active compound I was a short-acting drug and produced rapid clearance of parasites. The relatively high rate of recrudescence with Active compound I after three days of monotherapy highlighted the need to combine the drug with a long-acting drug.

Piperaquine phosphate was chosen as a partner drug and a Phase I double blind, randomized, parallel group, placebo controlled study was conducted in young healthy male subjects to investigate the safety, tolerability and pharmacokinetic profile of Active compound I and piperaquine phosphate after co-administration of multiple oral doses. The study comprised of three cohorts. Cohort I received an oral daily dose of 100 mg of Active compound I and 750 mg of piperaquine phosphate, Cohort II received an oral daily dose of 200 mg of Active compound I and 750 mg of piperaquine phosphate and Cohort III received an oral daily dose of 200 mg of Active compound I and 1000 mg of piperaquine phosphate. All three doses were administered once daily for three days in each cohort. No drug related adverse event was observed up to dose levels of 200 mg Active compound I and 750 mg of piperaquine phosphate. However, somnolence and vomiting were reported in dose level of 200 mg Active compound I and 1000 mg of piperaquine phosphate. Systemic exposures to Active compound I after repeated dosing was not appreciably different to that after single dose, hence no accumulation was observed for Active compound I upon 3 days repeated dosing of Active compound I - piperaquine phosphate combination. Exposures of Active compound I increased in a dose-proportional manner upon doubling the dose from 100 mg to 200 mg, when the dose of piperaquine phosphate was kept constant (Table 6).

Table 6: Geometric mean pharmacokinetic parameters of Active compound I (free base) following multiple oral co-administration of Active compound I and piperaquine phosphate to young healthy male subjects (n=6).

Cohort Study	T_{max} (h)		C_{max} (ng/ml)		$T_{1/2}$ (h)		AUC_{0-24} (ng.h/ml)		AUC_{0-t} (ng.h/ml)		R_o
	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	
I	3.11	4.42	73.63	78.87	3.60	3.86	540.18	623.74	547.82	637.36	1.15
II	4.56	5.31	164.20	148.51	4.69	5.86	1388.18	1527.63	1458.61	1683.30	1.10
III	4.29	4.06	180.99	163.04	5.14	5.46	1573.19	1772.53	1670.89	1940.10	1.13

R_0=Degree of accumulation calculated as (AUCo-24(Day 3)/AUCo-24 (Day 1))

Comparative Bioavailability Study of fixed-dose combination of Active compound I 150 mg + piperaquine phosphate 750 mg and co-pack formulations.

A single-dose, two-treatment, parallel design study comparing the bioavailability of fixed dose combination tablets of Active compound I 150 mg + piperaquine phosphate 750 mg with co-administered Active compound I 150 mg and piperaquine phosphate 750 mg was conducted as an open label, balanced, randomized, single-dose, two-treatment, parallel design in 36 healthy, adult, human, male subjects under fasting conditions. The pharmacokinetic parameters are presented in Tables 7 and 8. The results of this study suggested that the pharmacokinetics of Active compound I remained unaltered when administered in fixed-dose combination with piperaquine phosphate as compared to their co-administration as individual tablets.

Table 7: Geometric mean pharmacokinetic parameters of Active compound I (free base) following administration of fixed-dose combination (FDC) and co-pack formulations of Active compound I and piperaquine phosphate to young healthy male subjects.

T_{max} (h)		C_{max} (ng/ml)		AUC_{0-24} (ng.h/ml)		AUC_{0-t} (ng.h/ml)		$T_{1/2}$ (h)	
FDC	Co-pack	FDC	Co-pack	FDC	Co-pack	FDC	Co-pack	FDC	Co-pack
3.38	3.84	127.73	116.98	1143.01	1100.39	1146.70	1113.48	3.98	3.91

FDC: Fixed-dose combination tablet of Active compound I 150 mg and piperaquine phosphate 750 mg as one tablet (n=16); Co-pack: Three Active compound I 50 mg tablets and one piperaquine phosphate 750 mg tablet as individual tablets (n=17), AUC_{0-t} = AUC 0 to last measurable concentration (sampling up to 96 h).

Table 8: Geometric mean pharmacokinetic parameters of piperaquine following administration of fixed-dose combination (FDC) and co-pack formulations of Active compound I and piperaquine phosphate to young healthy male subjects.

T_{max} (h)		C_{max} (ng/ml)		AUC_{0-24} (ng.h/ml)		AUC_{0-t} (ng.h/ml)	
FDC	Co-pack	FDC	Co-pack	FDC	Co-pack	FDC	Co-pack
4.59	4.46	92.68	95.90	728.79	915.19	1431.48	1747.66

FDC: Fixed-dose combination tablet of Active compound I 150 mg and piperaquine phosphate 750 mg as one tablet (n=16); Co-pack: Three Active compound I, 50 mg tablets

and one piperaquine phosphate 750 mg tablet as individual tablets (n=17), AUCo-t= AUC 0 to last measurable concentration (sampling up to 96 h).

While several particular compositions have been described, it will be apparent that various modifications and combinations of the compositions detailed in the text can be made without departing from the spirit and scope of the invention.

We Claim:

1. A stable solid oral dosage form comprising;

(a) cis-adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino]carbonyl]-methyl]- 1',2',4'-trioxaspiro[4.5]decane hydrogen maleate (Active compound I);

(b) piperaquine; and

(c) one or more pharmaceutically acceptable excipients; wherein the dosage form is prepared by a dry process.

2. The stable solid oral dosage form according to claim 1, wherein the dosage form comprises:

(a) Active compound I in an amount of from about 5% to about 25%; and

(b) piperaquine in an amount from about 40% to about 80%, w/w based on the total weight of the dosage form.

3. The stable solid oral dosage form according to claim 1, wherein the pharmaceutically acceptable excipient is selected from the group consisting of binders, diluents, glidants/lubricants, disintegrants, surfactants and coloring agents.

4. The stable solid oral dosage form according to claim 3, wherein the diluent is microcrystalline cellulose.

5. The stable solid oral dosage form according to claim 1, wherein the dosage form has dissolution performance such that, more than 70% w/w of the Active compound I dissolves within 45 minutes, in a pH 4.5 acetate buffer with 2% tween 80, in USP type II apparatus.

6. The stable solid oral dosage form according to claim 1, wherein the Active compound I and piperaquine are present in a weight ratio of from about 1:1 to about 1:10.

7. The stable solid oral dosage form according to claim 1, wherein the Active compound I is present in a dose range of about 100 mg to about 300 mg and piperaquine present in a dose range of about 700 mg to about 850 mg.

8. The stable solid oral dosage form according to claim 1, wherein the dosage form comprises:

(a) Active compound I in an amount of from about 5% to about 25%;

(b) piperaquine in an amount of from about 40% to about 80%;

(c) diluent in an amount of from about 10% to about 40%;

(d) disintegrant in an amount of from about 1% to about 10%; and

(e) lubricant in an amount of from about 1% to about 5%, w/w based on the total weight of the dosage form.

9. The stable solid oral dosage form according to claim 1, wherein the dosage form comprises:

(a) Active compound I;

(b) piperaquine;

(c) microcrystalline cellulose;

(d) crospovidone; and

(e) magnesium stearate.

10. The stable solid oral dosage form according to claim 1, wherein the dosage form comprises:

(a) Active compound I in an amount of from about 5% to about 25%;

(b) piperaquine in an amount of from about 40% to about 80%, and

(c) microcrystalline cellulose in an amount of from about 10% to about 40%; w/w based on the total weight of the dosage form.

11. The stable solid oral dosage form according to claim 1, wherein the dosage form comprises Active compound I and microcrystalline cellulose in a weight ratio of from about 1:1 to about 1:5.

12. The stable solid oral dosage form according to claim 1, wherein the dosage form is selected from a group consisting of tablet, capsule, pill, granule and powder.

13. The stable solid oral dosage form according to claim 12, wherein the tablet is coated with one or more functional and or non-functional coating layers comprising film-forming polymers and coating additives.

14. The stable solid oral dosage form according to claim 13, wherein the coating additives comprise one or more of plasticizers, glidants or flow regulators, opacifiers and lubricants.

15. The stable solid oral dosage form according to claim 1, wherein the dosage form is processed and stored at a temperature below 27°C and relative humidity 50%.

16. The stable solid oral dosage form according to claim 1, wherein the dry process comprises direct compression or dry granulation.

17. The stable solid oral dosage form according to claim 1, wherein the dosage form is prepared by a process comprising the steps of:

(a) blending Active compound I, piperaquine, and one or more intragranular excipients;

(b) milling, grinding or sieving the blend by roller compaction to form granules;

(c) blending the granules with one or more extragranular excipients; and

(d) compressing the blend into tablets or filling into capsules.

18. The stable solid oral dosage form according to claim 1, wherein the dosage form is prepared by a process comprising the steps of:

(a) blending Active compound I, piperaquine, and one or more intragranular excipients;

(b) granulating the blend by slugging;

(c) blending the granules with one or more extragranular excipients; and

(d) compressing the blend into tablets or filling into capsules.

19. The stable solid oral dosage form according to claim 1, wherein the dosage form is prepared is prepared by a process comprising the steps of:

(a) blending Active compound I, piperaquine, and one or more pharmaceutically acceptable excipients; and

(b) directly compressing the blend into tablets or filling into capsules.

20. The stable solid oral dosage form according to claim 1, wherein the dosage form is prepared by a process comprising the steps of:

(a) granulating a blend of one or more excipients;

(b) drying the excipient granules;

(c) blending excipient granules with Active compound I and piperaquine; and

(d) compressing the blend into tablets or filling into capsules.

21. A stable solid oral dosage form comprising:

(a) 150 mg of Active compound I and

(b) 750 mg of piperaquine,

wherein the dosage form is administered once a day for three days.

22. The stable solid oral dosage form according to claim 21, wherein the first dose of the dosage form is administered immediately on diagnosis, the second dose about 24 hours after the first dose, and the third dose about 24 hours after the second dose.

23. A method of treatment of malaria, the method comprising administering a stable oral solid dosage form comprising:

(a) Active compound I;

(b) piperaquine; and

(c) one or more pharmaceutically acceptable excipients

wherein the dosage form is prepared by a dry process.

24. A method of treating malaria comprising administering a stable solid oral dosage form comprising;

(a) 150 mg Active compound I and

(b) 750 mg of piperaquine

wherein the dosage form is administered once a day for three days.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053614

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/357 A61K31/496 A61K9/20 A61P33/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/123314 A2 (RANBAXY LAB LTD [IN] ; MADAN SUMIT [IN] ; TYAGI PUNEET [IN] ; TREHAN ANUP) 23 November 2006 (2006-11-23) page 17 - page 18; examples 3,4 claims 1-20	1-24

-/- .

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2012	23/10/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053614

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SNYDER ET AL: "In vitro and in vivo interacti on of syntheti c peroxi de RBxlll60 (0Z277) wi th pi peraqui ne i n Pl asmodi um model s", EXPERIMENTAL PARASITOLOGY, NEW YORK, NY, US, vol . 115, no. 3, 2 December 2006 (2006-12-02) , pages 296-300, XP005724230, ISSN: 0014-4894, D0I: 10. 1016/J . EXPPARA.2006.09 .016 page 299, ri ght-hand col umn, l ast l i ne - page 300, l i ne 2 abstract	1-24
Y	W0 2007/132438 A2 (RANBAXY LAB LTD [IN] ; SHINGATGERI VYAS MADHAVRA0 [IN] ; UDUPA VENKATESH) 22 November 2007 (2007-11-22) cl aims 1-6	1-24
X,P	VALECHA NEENA ET AL: "Arterol ane Mal eate Pl us Pi peraqui ne Phosphate for Treatment of Uncompl i cated Pl asmodi um fal ci parum Mal ari a: A Comparati ve, Mul t i center, Randomi zed Cl i ni cal Tri al", CLINICAL INFECTIOUS DISEASES, vol . 55, no. 5, 14 May 2012 (2012-05-14) , pages 663-671 URL, XP009163781 , the whol e document	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053614

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006123314 A2	23-11-2006	EP 1898901 A2	19-03-2008
		US 2009042821 A1	12-02-2009
		WO 2006123314 A2	23-11-2006
WO 2007132438 A2	22-11-2007	BR PI0711585 A2	16-11-2011
		CN 101472582 A	01-07-2009
		EP 2026795 A2	25-02-2009
		US 2009306091 A1	10-12-2009
		WO 2007132438 A2	22-11-2007
		ZA 200809768 A	29-07-2009