

Solid pharmaceutical compositions containing miltefosine for oral administration in the treatment of leishmaniasis

The present invention relates to new solid pharmaceutical compositions containing hexadecylphosphocholine (miltefosine) for oral administration in the treatment of leishmaniasis, a process for the manufacture of said pharmaceutical composition, a dosage scheme for oral administration of said pharmaceutical composition in the treatment of leishmaniasis, and finally a combination comprising said solid pharmaceutical composition, an antiemeticum, and/or an antidiarrhoeal

Leishmaniasis is a name for various tropical diseases which are caused by flagellates of the genus Leishmania and is transmitted by various blood-sucking insects. The manifestations of leishmaniasis may be visceral (kala-azar), mucocutaneous (american leishmaniasis) or cutaneous (Aleppo boil or diffuse cutaneous leishmaniasis). The incubation period is weeks or months. A very high mortality rate is observed in untreated cases, in particular with kala-azar and american leishmaniasis.



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Prior to the present invention there was no medicament available in the state of the art for oral therapy of leishmaniasis. The known agents in the standard therapy for the treatment of leishmaniasis, i.e. pentavalent antimony compounds (e.g. sodium stibogluconate) and aromatic diamidines, had to be administered by i.v. injection, thereby not only causing severe side-effects due to their high toxicity, but also putting up with the risk of infections.

Leishmania is a parasitic disease which often is encountered in geographical areas with an extreme tropical climate and where medical care is complicated by insufficient transport ways. Any medication containing miltefosine for the treatment of leishmania, therefore, has to take account of these harsh environmental conditions.

The usability of milefosine in the oral and topical treatment of leishmaniasis was for the first time described by Eibl et al. in the German unexamined patent application no. P 41 32 344 filed September 27, 1991.

Although obtainable in dry form as crystalline plates with a definite melting point of above 200 °C, miltefosine is difficult to handle due to its high hygroscopicity. The incorporation of water molecules may result in an increase in weight of up to 30 % by weight, melting point depression and agglomeration and agglutination of the crystals. The water-containing miltefosine exhibits insufficient workability to be further processed into solid pharmaceutical compositions, such as tablets, capsules or sachets. In particular the flowability of water-containing miltefosine is insufficient. Satisfactory flowability, however, is one of the essential prerequisites for manufacturing solid pharmaceutical compositions on an industrial scale.

In addition, anhydrous miltefosine exhibits a significant tendency of electrostatic charging, particularly when stirred in dry state. Electrostatic-charged miltefosine, too, exhibits insuffient flowabilty to be further processed into solid pharmaceutical compositions. Moreover, any electrostatic charging raises significant safety concerns due to the accompanied risk of both explosion and sensitive electronical parts being damaged.

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In an attempt to overcome the aforementioned problem in the preparation of solid pharmaceutical compositions containing miltefosine, Eibl et al. suggested coating miltefosine onto the surface of silicon dioxide particles by evaporating to dryness a suspension of 1 part by weight of silicon dioxide in a solution containing 1 part by weight of miltefosine. The resulting solid dispersion as suggested by Eibl et al. indeed exhibits sufficient flowability to be filled into capsules, at least as far as a laboratory scale was concerned. However, the process as described by Eibl et al. is bound to the use of a highly volatile as well as non-inflammable (due to the electrostatic charging) solvent. For all practical purposes, there are only two solvents available in the state of the art which meet these requirements, namely methylene chloride and chloroform. However, halogenated hydrocarbons, in particular chloroform, are classified as toxic and cancerogenic compounds. In addition, halogenated hydrocarbons are enriched in the fat tissues and only slowly metabolized. Thus, a development of a solid pharmaceutical composition according to the disclosure by Eibl et al. has only little chance of being approved by the competent health authorities, at least as far as humans and animals forming part of the food chain are concerned.

From the foregoing it follows that there was a long-lasting need for a solid pharmaceutical composition for oral administration in the treatment of leishmania. To solve this problem was the object of the present invention.

Surprisingly and unexpectedly, it has now been found according to one aspect of the present invention that the aforementioned problems can be solved by simply physically mixing hexadecylphosphocholine, at least one flowability-controlling agent and/or lubricant selected from the group consisting of highly dispersed silicon dioxide, talc, magnesium stearate and mixtures thereof, and at least one filler selected from the group consisting of lactose, microcrystalline cellulose and mixtures thereof.

The subject matter of the present invention is new and non-obvious over the pertinent prior art since no carrier particles or granulating solvent are necessary any longer to obtain a solid pharmaceutical composition containing miltefosine with sufficient flowability. According to the present invention, by simply physically blending of miltefosine, a flowability-controlling agent and/or lubricant, and at least one filler can provide a solid pharmaceutical blend having sufficient flowability to be processed further into, for example, capsules, tablets or sachets.

In contrast, according to the teaching of Eibl et al., the skilled person would have tried to achieve a desired flowability either by way of granules by using a granulating solvent other than water (due to the hygroscopicity of miltefosine) or by way of solid dispersions. In the latter case, a large excess of silica gel is necessary.

Therefore, the subject matter of the present invention is new and inventive over the pertinent prior art.

In a preferred embodiment, the solid pharmaceutical composition according to the present invention can be filled into capsules, preferably hard gelatine capsules, or pressed into tablets or effervescent tablets, or filled into sachets as drinkable blend or effervescent blend.

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The content of miltefosine per dosage unit is in the range of 10 to 800 mg, preferably in the range of 10 to 500 mg, more preferably in the range of 50 to 250 mg. The most preferred content is in the range of 50 to 150 mg.

Suitable flowability-controlling agents are, for example, highly disperse or colloidal silicon dioxide (e.g. Aerosil ® such as Aerosil ® V200; DEGUSSA AG, Germany), magnesium stearat, talcum, talcum siliconisatum, calcium arachinate, cetyl alcohol, myristyl alcohol, and mixture thereof. Lubricants that may for example be used are magnesium stearate or other stearates like calcium stearate, D,L-Leucin, talcum, stearic acid, lauric acid, polyglycols (mean molecular weight 3000-35000), fatty alcohols or waxes.
The preferred ratio between miltefosine and flowability-controlling agent and/or lubricant is 1 part by weight of miltefosine to 0.01 - 0.6 parts by weight of the flowability-controller.

Anti-adhesion agents that may for example be used are: glycols, starch, talcum, talcum siliconisatum, aluminium stearate, stearic acid, magnesium stearate, calcium stearate or D,L-leucin.

Suitable flow-controlling agents, lubricants and antiadhesion agents are for example listed in the following textbooks:
W.A. Ritschel, DIE TABLETTE, Editio Cantor Verlag, page 125, 1st edition 1966;
Sucker, Fuchs, Speiser, PHARMAZEUTISCHE TECHNOLOGIE, g. Thieme Verlag, Stuttgart, pages 334 to 336, 1st edition 1978;
Münzel, Büchi, Schultz, GALENISCHES PRAKTIKUM, Wissenschaftliche Verlagsanstalt, Stuttgart, page 731, 1st edition, 1959;
R. Voigt, LEHRBUCH DER PHARMAZEUTISCHEN TECHNOLOGIE, 4th edition, Verlag Chemie, Weinheim, page 195, 1st edition 1982;
P.H. List, ARZNEIMITTELLEHRE, Wissenschaftliche Verlagsanstalt, Stuttgart, page 86, 1st edition 1976.

The solid pharmaceutical compositions according to the invention may also contain binding agents such as gelatine, cellulose, cellulose ethers, amyloses, dextrose, polyglycols, tragacanth., pectins, alginates, polyvinylpyrrolidone.

The solid pharmaceutical compositions according to the invention may also contain disintegrating agents such as for example: starches (e.g. corn starch), modified starch (for example sodium starch glycolate, starch 1500), pectins, betonite, cellulose, cellulose derivatives (for example carboxymethyl celluloses), alginates, polyvinyl pyrrolidones, ultraamylopectin, cross-linked polyvinyl pyrrolidone or cross-linked carboxymethyl cellulose (Ac-Di-Sol/FMC).

Suitable fillers are, for example, lactose (for example, spray-dried), glucose, fructose, calcium phosphates, calcium sulfates, calcium carbonates, starch, modified starch, sugar alcohols such as sorbitol or mannitol, cellulose derivatives, saccharose, microcrystalline cellulose, and mixtures thereof.
The preferred ratio between miltefosine and the filler is 1 part by weight of miltefosine to 0.1 - 120 parts by weight of the filler.

According to a further aspect of the invention, a process for the manufacture of the pharmaceutical composition according to the present invention is provided, comprising the steps of

(a) blending of miltefosine, the flow-controlling agent and the filler, optionally together with further auxiliary agents, thereby obtaining a pharmaceutical composition having sufficient flowability, and
(b) filling the obtained blend into capsules or sachets, or alternatively, compressing the obtained blend to tablets.

The production of an oral pharmaceutical composition according to the present invention can be carried out by mixing or homogenizing miltefosine with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at temperatures between 20 and 120°C and, if desired, in order to prepare formulations which contain 10 to 800 mg of miltefosine in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances. The active substance can for example be mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol. The mixture obtained is granulated, if desired, with an aqueous solution containing for example gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidon-vinyl acetate copolymerisate or/and polyoxyethylene sobianmonooleate, as constituent and the granulate is homogenized, if desired, with on or several of the aforementioned auxiliary substances. Subsequently this mixture can be pressed into tablets or filled into into capsules whereby the tablets or capsules each contain 10 to 800 mg of miltefosine in one dosage unit.

The manufacture of the capsules and tablets occurs for example between 15 °C and 26 °C, preferably between 18 °C and 22 °C. The relative humidity in the production rooms should preferably not exceed 40%.

The preparation of the solid pharmaceutical compositions according to the invention is effected in a conventional manner, it also being possible to use conventional and customary pharmaceutical auxiliary substances and other conventional carriers and diluents.

According to the invention, the process for manufacturing the pharmaceutical compositions may further comprise the step of granulating the composition having sufficient flowability as obtained according to step (a) prior to step (b) by per se known methods. Granulation can be effected according to methods known per se in the art (see e.g. Hagers Handbuch der pharmazeutischen Praxis, 5th edition, Springer Verlag, 1991, pages 722-742). The blend can be melted with a liquid and if required the moist compound can then passed through a strainer. The further processing steps are drying, screening, mixing with further excipients and filling in sachets or capsules, or compressing into tablets. The blend can also be compounded or extruded according to the prior art in order to get a granulate.

Carrier and excipients that may for example be considered are those which are recommended or quoted in the following literature references as auxiliary substances for pharmacy, cosmetics and related fields: „ Ullmanns Encyklopädie der technischen Chemie", Volume 4 (1953), pages 1 to 39; Journalof Pharmaceutical Sciences, Volume 52 (1963), page 918 et seq.; H.v.Czetsch-Lindenwald, „Hilfsstoffe für Pharmazie und angrenzende Gebiete"; Pharm. Ind. issue 2 (1961), page 72 et

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seq.; Dr. H. P. Fiedler, „Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete" cantor KG, Aulendorf in Württemberg 1981.

Examples thereof are gelatine, natural sugars such as unrefined sugar or lactose, lecithin, pectin starches (for example corn starch), cyclodextrines and cyclodextrine derivates, polyvinyl pyrrolidone, polyvinyl acetate, gelatine, gum arabic, alginic acid tylose, talcum, lycopodium, silica gel (for example colloidal), cellulose, cellulose derivates (for example cellulose ether in which the cellulose hydroxy groups are partially etherified with lower saturated aliphatic alcohols and/or lower saturated aliphatic oxyalcohols, for example methyloxypropyl cellulose, methyl cellulose , hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate); fatty acids as well as magnesium, calcium or aluminium salts of fatty acids with 12 to 22 carbon atoms, in particular saturated ones (for examples stearates), emulsifiers, oils and fats, in particular vegetable fats (for example peanut oil, castor oil, olive oil, sesame oil, cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod liver oil, in each case also hydrogenated; mono-, di- and triglycerides of saturated fatty acid $C_{12}H_{24}O_2$ to $C_{18}H_{36}O_2$ and their mixtures, pharmaceutically acceptable single or multivalent alcohols and polyglycols such as polyethylene glycols as well as derivates thereof, esters of aliphatic saturated or unsaturated fatty acids (2 to 22 carbon atoms, in particular 10 - 18 carbon atoms) with monovalent aliphatic alcohols (1 to 20 carbon atoms) or multivalent alcohols such as glycols, glycerine, diethylene glycol, pentaerythritol, sorbitol, mannitol and so on, which may optionally also be etherified, esters of citric acid with primary alcohols, acetic acid, benzylbenzoate, dioxolanes, glycerine formals, tetrahydrofurfuryl alcohol, polyglycol ether with C_1-C_{12}-alcohols, dimethylacetamide, lactamides, lactates, ethyl carbonates, silicons (in particular medium-viscous polydimethylsiloxanes), calcium carbonate, sodium, carbonate, calcium phosphate, sodium phosphate, magnesium carbonate and the like.

Other excipients that may be used are substances which aid disintegration (so called disintegrants) such as:
cross-linked polyvinyl pyrrolidone, sodium carboyxmethyl starch, sodium carboxymethyl cellulose or microcristalline cellulose.

Powders are manufactured in the following manner: Miltefosine, at least one flowability-controlling agent and/or lubricant, at least one filler, and optionally a flavouring agent and/or sweetener are blended and filled into sachets (bags) of the appropriate dosage unit. In use, the whole content of a bag, or alternatively a part of it, are stirred into water or fruit juice and swallowed. This method makes it easy to apply any level of dosage by the peroral route.

To prepare an effervescent tablet or an effervescent blend, miltefosine, at least one flowability-controlling agent and/or lubricant, and at least one filler are blended in conventional manner with a carbonate or an acid component and the mixture obtained is pressed into tablets or filled into bags, optionally after addition of flavourings, of still missing acid components or of the carbonate as well as other flow-controlling agents and lubricants. Likewise, administration is performed by taking the tablet or blend in water.

The solid pharmaceutical compositions according to the invention may also contain flavouring, sweetening and/or aromatic substances.

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Aromatic substances are: pineapple, apple, apricot, raspberry, cherry, cola, orange, passion fruit, lemon, grapefruit, vanilla, chocolate. The following substances may be used as sweeteners: saccharin and its sodium salt, cyclamic acid and its sodium salt, ammonium glycyrrhizinate, fructose, xylitol, sorbitol, mannitol, aspartane, acesulfam-K.

The effervescent powder or chewable or effervescent tablets are prepared using conventional processes as described in the literature (for example in the standard reference work by Sucker, Fuchs, and Speiser (edit.), Pharmazeutische Technologie, Thieme Verlag, Stuttgart). The preparation (all steps apart from drying) is carried out, for example, at temperatures between 10 °C and 80 °C, preferably 18 °C to 50 °C, in particular 20 °C to 30 °C.

The production of miltefosine is described in detail in the examples for hexadecyl-phosphocholine as described in the German unexamined patent application no. P 41 32 344 Further methods for the production and purification of miltefosine are described, for example, in German unexamined patent applications nos. DE-A 27 52 125, DE-A 36 41 379, DE-A 36 41 491, DE-A 40 13 632, DE-A 36 41 377, the literature cited in these or in earlier patent applications or patent specifications is incorporated herewith by reference.

According to a further aspect of the present invention, a dosage scheme for the treatment of leishmaniasis in humans by oral administration of the pharmaceutical composition according to the present invention is provided.

In a preferred embodiment of the invention, the following dosage scheme in the treatment of leishmania in humans by oral administration is suitable:

Total daily dosage: 10-250 mg, preferably 50-150 mg a.i. miltefosine (a.i. = active ingredient);

Single or multiple daily dosage: a total daily dosage of 10-50 mg a.i. is preferably administered as a single daily dosage; a dosage between 50-250 mg a.i., preferably between 50-150 mg a.i. is administered orally as a multiple daily dosage, preferably as a twice daily dosage (100 mg a.i. total daily dosage) or three times daily dosage (150 mg a.i. total daily dosage); With regard to patient compliance, a 4-5 times divided daily dosage is generally regarded as an upper limit. For cure reasons, however, other than 1-5 times divided daily doses can be applied as well.

In a preferred embodiment, multiple daily doses are administered in equal portions (e.g. 100 mg a.i./day = 2 x 50 mg a.i./day or 150 mg a.i./day = 3 x 50 mg a.i./day).

Period of time of therapy: 2-6 weeks, preferably 4 weeks.

According to a further aspect of the invention, a dosage scheme for the treatment of leishmaniasis in mammalians other than humans by oral administration of the pharmaceutical composition according to the present invention is provided.

All mammalian animals can be treated by the invention, for example, small companion animals such as for example dogs, all rodents and hamsters. The treatment can be performed in the natural surroundings of the animals or in selected surroundings like animal hospitals or veterinarian offices, with the former being

preferred. All leishmania species can be treated by the inventive dosage scheme, especially leishmania major and leishmania infantum. According to the dosage scheme of the invention, the total daily dosage in the treatment by oral administration is in the range of 1-15 mg a.i. miltefosine per kg body weight of the animal (mg a.i./kg). In a preferred embodiment, therapy is started with an initial total single dosage (loading dosage) in the range of 3-15, preferably 5-10 mg a.i./kg, and thereafter continued with a total daily dosage (maintenance dosage) in the range of 1-10, preferably 3-5 mg a.i./kg. The period of time for treatment is in the range of 2-8, preferably 4-5 weeks.

According to a further aspect of the invention, a combination of the pharmaceutical composition according to the invention with an antiemeticum and/or antidiarrhoeal for oral administration in the treatment of leishmaniasis is provided.

In a preferred embodiment of the invention, the pharmaceutical composition according to the invention is administered in combination with an antiemeticum and/or an antidiarrhoeal. The administration can be performed simultaneously or subsequently. The antiemeticum and the antidiarrhoeal can be administered independently of each other. The antiemeticum and/or antidiarrhoeal can either be contained in the pharmaceutical composition according to the invention or be contained in an pharmaceutical formulation independent thereof.

Suitable antiemetica are, for example, 5-HT3-receptor antagonists, substituted benzamides, corticosteroids, antihistaminica, neuroleptica of the phenothiatine-type, neuroleptica of the butyrophenone-type, benzodiazepines and cannabinoids. Preferred antiemetica are, inter alia, metoclopramid, domperidon and alizaprid.

Suitable antidiarrhoeal are, inter alia, the opioids, such as loperamid.

The solid oral pharmaceutical compositions according to the invention are preferably useful in the treatment of leishmaniasis. Other protozoal diseaes which can be treated by the agent according to the present invention are for instance malaria, trypanosomiasis, toxoplasmosis, babesiosis, amoebic dysentery and lambliasis. The agents according to the present invention are in particular suitable for those diseases in which the pathogen is present in inner organs such as the liver, spleen or kidney, in lymph knotes, bone marrow, and blood.

It is intended to elucidate the invention further by the following examples without the invention being restricted by these examples.

I. Examples for solid oral pharmaceutical formulations according to the invention

Example 1: Hard gelatine capsule (content: 10 mg miltefosine)

100 g hexadecylphosphocholine, 808,50 g lactose, 448,50 g microcrystalline cellulose, 26 g talcum and 13 g highly dispersed silicon dioxide are passed through a sieve with a mesh number of 0.8 mm and then are homogenized in a suitable mixer over 30 minutes. Then 4 g magnesium stearate (0.8 mm sieve) is added and the components are blended over further 5 minutes. The obtained mixture is filled in a

known way in portions of 140 mg into gelatin hard capsules of 50 mg weight by using a suitable capsules machine.
Each capsule as obtained (total weight: 190 mg) contains 10 mg hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the filling mixture is 1 : 0.4 : 12.4 (parts by weight).

Example 2: Hard gelatine capsule (content: 50 mg miltefosine)

258 g hexadecylphosphocholine, 430 g lactose, 241 g microcrystalline cellulose, 14 g talcum, 7 g highly dispersed silicon dioxide and 2 g magnesium stearate were blended according to the process as described in Example 1. The thus obtained filling mixture is filled in portions of 185 mg into gelatine hard capsules of 59 mg weight in a known way by using a suitable capsules machine.
Each capsule as obtained (total weight: 244 mg) contains 50 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agents and lubricants : fillers in the filling mixture is 1 0.09 : 2.6 (parts by weight).

Example 3: Hard gelatine capsule (content: 100 mg miltefosine)

1000 g hexadecylphosphocholine, 584 g lactose, 345 g microcrystalline cellulose, 50 g talcum, 15 g highly dispersed silicon dioxide and 6 g magnesium stearate were blended according to the process as described in Example 1.
The thus obtained filling mixture is filled in portions of 200 mg into gelatin hard capsules of 76 mg weight in a known way by using a suitable capsules machine.
Each capsule as obtained (total weight: 276 mg) contains 100 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.07 : 0.9 (parts by weight).

Example 4: Hard gelatine capsule (content: 150 mg miltefosine)

150 g hexadecylphosphocholine, 30 g lactose, 15 g microcrystalline cellulose, 3 g talcum, 2 g highly dispersed silicon dioxide and 1 g magnesium stearate were blended according to the process as described in Example 1. The thus obtained filling mixture is filled in portions of 201 mg into gelatin hard capsules of 76 mg weight in a known way by using a suitable capsules machine.
Each capsule as obtained (total weight: 277 mg) contains 150 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.04 : 0.3 (parts by weight).

Example 5: Hard gelatine capsule (content: 200 mg miltefosine)

200 g hexadecylphosphocholine, 80 g lactose, 50 g microcrystalline cellulose, 4 g talc, 5 g highly dispersed silicon dioxide and 10 g magnesium stearate were blended according to the process as described in Example 1. The thus obtained filling mixture is filled in portions of 349 mg into gelatin hard capsules of 97 mg weight in a known way by using a suitable capsules machine.

Each capsule as obtained has a total weight of 446 mg and contains 200 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.095 : 0.65 (parts by weight).

Example 6: Hard gelatine capsule (content: 250 mg miltefosine)

250 g hexadecylphosphocholine, 80 g lactose, 50 g microcrystalline cellulose, 5 g talc, 5 g highly dispersed silicon dioxide and 15 g magnesium stearate were blended according to the process as described in Example 1. The thus obtained filling mixture is filled in portions of 405 mg into gelatin hard capsules of 97 mg weight in a known way by using a suitable capsules machine.
Each capsule as obtained has a total weight of 502 mg and contains 250 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.1 : 0.52 (parts by weight).

Example 7: Tablets (content: 250 mg of hexadecylphosphocholine)

50 g of hexadecylphosphocholine, 24.25 g of microcrystalline cellulose and 22.00 g of anhydrous dicalcium phosphate are sieved and blended. 3.75 g of magnesium stearate are sieved and added to the blend. Then the mixture is blended again. The resulting blend is compressed into tablets each weighing 500 mg. One tablet contains 250 mg hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.07 : 0.925 (parts by weight).

Example 8: Tablets (content: 30 mg of hexadecylphosphocholine)

23 g of hexadecylphosphocholine, 23 g of microcrystalline cellulose, 52 g of spray-dried lactose are sieved and blended. 1g of colloidal silicon dioxide and 1 g of magnesium stearate are added. The mixture is then blended again.
The resulting blend is compressed into tablets each weighing 130.5 mg. One tablet contains 30 mg hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.087: 0.31 (parts by weight).

Example 9: Effervescent tablets and blend (content of hexadecylphosphocholine: 250 mg)

1700 g of granular sodium bicarbonate are given in an oven and heated at 100 °C for 60 min. After cooling to room temperature the converted bicarbonate is mixed with 160 g of granular monobasic calcium phosphate, 1030 g of granular anhydrous citric acid, 100 g of talcum and 50 g of magnesium stearate. To the resulting mixture are added 300 g of hexadecylphosphocholine und blended for 10 minutes.
The resulting effervescent blend is compressed into tablets each weighing 278 mg. One effervescent tablet contains 250 mg of hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.50 : 0.53 (parts by weight).

Alternatively, the effervescent blend can be filled in an amount of 278 mg into sachets thus obtaining an effervescent blend.

Example 10: Effervescent tablets and blend (content: 50 mg of hexadecylphosphocholine)

1 600 g of granular sodium bicarbonate are given in an oven and heated at 100 °C for 60 min. After cooling to room temperature the converted bicarbonate is mixed with 150 g of granular monobasic calcium phosphate, 900 g of granular anhydrous citric acid, 80 g of talcum and 30 g of magnesium stearate. To the resulting mixture are added 200 g of hexadecylphosphocholine und blended for 10 minutes. The resulting mixture is compressed into tablets each weighing 740 mg. One effervescent tablet contains 50 mg of hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.55 : 0.75 (parts by weight).

Alternatively, the effervescent blend can be filled in an amount of 740 mg into sachets thus obtaining an effervescent blend.

Example 11: Drinkable blend (Sachets) (content: 50 mg of hexadecylphosphocholine)

5 g of hexadecylphosphocholine, 308 g of lactose, 280 g of microcrystalline cellulose, 5 g of saccharin and 2 g of colloidal silicon dioxide are blended. The blend is filled into sachets. One sachet weighs 6 g and contains 50 mg of hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the blend is 1 : 0.4 : 117.5 (parts by weight).

Example 12: Drinkable blend (Sachets) (content: 100 mg of hexadecylphosphocholine)

10 g of hexadecylphosphocholine, 200 g of lactose, 250 g of microcrystalline cellulose, 7 g of saccharin and 3 g of colloidal silicon dioxide are blended. The blend is filled into sachets. One sachet weighs 4.7 g and contains 100 mg of hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the blend is 1 : 0.3 : 45 (parts by weight).

Example 13: Drinkable blend (Sachets) (content: 200 mg of hexadecylphosphocholine)

20 g of hexadecylphosphocholine, 306 g of lactose, 403 g of microcrystalline cellulose, 5 g of saccharin and 6 g of colloidal silicon dioxide are blended. The blend is filled into sachets. One sachet weighs 7 4 g and contains 200 mg of hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the blend is 1 : 0 3 : 35.5 (parts by weight)

II. Results of clinical studies in the treatment of leishmaniasis where capsules according to the present invention were administered perorally

In the following, the abbreviations mean:
once qod = one administration every other day;
BID qod = two administrations every other day;
BID = two daily administrations;
TID = three daily administrations;
QID = four daily adminstrations;

Miltefosine (MILT, hexadecylphosphocholine, ASTA Medica), an antineoplastic alkylphospholipid, is active in experimental visceral leishmaniasis (VL). To test oral MILT in human VL, 30 male Indian patients from Bihar (age > 14 years; 18 of the 30 were antimony (Sb) failures) with splenic aspirate-positive VL were treated in 6 groups of 5 patients each (Groups A-F) for 28 days with escalating doses by oral administration of capsules according to example 1. (A) 50 mg once qod (qod = quantity every other day), (B) 50 mg BID qod (BID = twice per day), and then daily using 50 mg (C) BID (100 mg/d), (D) TID (150 mg/d), (E) QID (200 mg/d), and (F) 5x per day (250 mg/d).

16 patients were afebrile by day 7. Day 14 results in 30 patients: 25 afebrile, 25 decreased spleen size, 28 with negative spleenic aspirates (apparent parasitologic cure); 21 of 30 showed all 3 responses and were thus considered apparent cures.
1 Group F patient died on day 21 (drug stopped day 19) with severe vomiting and diarrhea (possibly drug- or intercurrent gastroenteritis-associated), dehydration, and renal failure. Mild vomiting or diarrhea lasting 3 - 7 days developed in most patients in Groups B - E.
1 patient in Group E and 3 more in Group F were removed on days 7, 7, 8 and 10 because of vomiting. 200 mg/d was therefore the maximum tolerated daily dose . There was no hematologic toxicity.
1 Group F patient developed increased hepatic transaminases (resolved).
One day 28, 29 of 29 patients (100 %) were apparent cures including the 4 who recieved < 10 days of therapy and were not further treated.
Within 6 months, 7 of 29 apparent cures relapsed (A-3/5, B-3/5, D-1/5); thus, 6 of 7 relapses were in the low-dose, qod-dosing groups (A,B). Within 6 months, apparant cure (no relapse, parasite-free bone marrow aspirate) has been achieved in 21 of 26 patients (A-2/5, B-2/5, C-5/5, D-4/5, E5/5); 1 patients is still in follow up; of the first 21 patients with definite cure 14 had failed prior therapy with antimony.

The found results demonstrate that the solid pharmaceutical compositions and the dosage scheme according to the present invention are effective in the treatment of leishmaniasis by peroral administration. Apparant cures were even observed in patients with the increasing problem of antimony-unresponsive visceral infection.

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New Claims 1 – 23:

1. Solid pharmaceutical composition for oral administration in the treatment of leishmaniasis comprising miltefosine, a flow-controlling agent and/or lubricant, and a filler.

2. Solid pharmaceutical composition according to claim 1, characterized in that the solid composition is selected from the group consisting of capsules, tablets, effervescent tablets, effervescent blend and sachets (drinkable blend).

3. Solid pharmaceutical composition according to claims 1 or 2, characterized in that the flow-controlling agent is selected from the group consisting of silicon dioxid, talc, magnesium stearate and mixtures thereof.

4. Solid pharmaceutical composition according to one of claims 1 to 3, characterized in that the filler is selected from the group consisting of a cellulose, lactose, mannitol, a calcium phosphat and mixtures thereof.

5. Solid pharmaceutical composition according to one of claims 1 to 4, characterized in that the ratio between hexadecylphosphocholine (HPC) and the flow-controlling agent and/or lubricant is 1 part by weight of HPC and 0.01 - 0.6 parts by weight of flow-controlling agent and/or lubricant.

6. Solid pharmaceutical composition according to one of claims 1 to 4, characterized in that the ratio between hexadecylphosphocholine (HPC) and the filler is 1 part by weight of HPC and 0.1 - 120 parts by weight of filler.

7. Solid pharmaceutical composition according to one of claims 1 to 6, characterized in that a solid pharmaceutical composition having sufficient flowability is obtained by simply physically blending miltefosine, a flow-controlling agent and/or lubricant, and a filler.

8. Solid pharmaceutical composition according to one of claims 1 to 7, characterized in that optionally the obtained pharmaceutical composition having sufficient flowability can be granulated prior to its processing into tablets, capsules or sachets.

9. Solid pharmaceutical composition according to one of claims 1 to 8, characterized in that it can further comprise one or more excipients (auxiliary agents) selected from the group consisting of disintregrating agents, a bindung agent (binders), anti-adherent agents, carriers, diluents, effervescent mixtures (e.g. a carbonate component and an acid component), flavouring agents, sweeteners, aromatic agents.

10. Process for manufacturing a solid pharmaceutical composition according to one of claims 1 to 9, comprising the steps of
(a) blending of miltefosine, the flow-controlling agent and the filler, optionally together with further auxiliary agents, thereby obtaining a pharmaceutical composition having sufficient flowability, and

(b) filling the obtained blend into capsules or sachets, or alternatively, compressing the obtained blend to tablets.

11. Process according to claim 10, characterized in that the composition having sufficient flowability as obtained according to step (a) can be granulated by per se known methods prior to step (b).

12. Use of miltefosine for the preparation of a medicament for the treatment of leishmaniasis in humans by oral administration, whereby a total daily dosage in the range of 10 to 250 mg a.i. miltefosine is administered orally over a period of time of 2 to 6 weeks.

13. Use according to claim 12, characterized in that the total daily dosage is about 50 to about 150 mg a.i. miltefosine.

14. Use according to claims 12 or 13, characterized in that administration is continued on a daily base for period of time of about 4 weeks.

15. Use according to one of claims 12 to 14, characterized in that the oral administration takes place once, twice or trice per day when the total daily dosage is 50, 100 and 150 mg a.i. miltefosine, respectively.

16. Use according to claim 15, characterized in that multiple daily doses are administered in equal portions (e.g. 100 mg a.i./day = 2 x 50 mg a.i./day, 150 mg a.i./day = 3 x 50 mg a.i./day).

17. Use of miltefosine for the preparation of a medicament for the treatment of leishmaniasis in mammalians other than humans by oral administration, whereby a total daily dosage in the range of 1 to15 mg a.i. miltefosine per kg body weight of the mammalian (mg a.i./kg) is administered over a period of time in the range of 2-8 weeks.

18. Use according to claim 17, characterized in that the initial single daily dosage (loading dosage) is in the range of 3-15 mg a.i./kg and the following daily dosages (maintenance dosages) are in the range of 1-10 mg a.i./kg.

19. Use according to claim 18, characterized in that the loading dosage is in the range of 5-10 mg a.i./kg.

20. Use according to claim 18, characterized in that the maintenance dosage is in the range of 3-5 mg a.i./kg.

21. Use according to one of claims 17 to 20, characterized in that the period of time for oral administration is 4 weeks.

22. Use according to one of claims 17 to 21, characterized in that small companion animals, such as dogs, all rodents and hamsters, are treated thereby.

23. Pharmaceutical composition comprising a pharmaceutical composition containing miltefosine, an antiemeticum and/or antidiarrhoeal for use in the treatment of leishmaniasis.