12504
Griseofulvin

PATENT SPECIFICATION

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810,378

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COMPLETE SPECIFICATION

Fungicidal Compositions Containing Griseofulvin

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to fungicidal compositions and more particularly it relates to fungicidal compositions comprising griseofulvin for the treatment of fungus diseases of man and animals.

Griseofulvin is a known antibiotic and it is known to be useful in the treatment of certain fungus diseases of plants. It has not hitherto been used in the treatement of fungus diseases of man and animals.

Furthermore many important fungus diseases of man and animals are skin diseases, for example ringworm and athlete's foot, and these are commonly treated by topical application of medicaments in the form of ointments and the like. Our co-pending Application No. 28904/56 (Serial No. 810,377) of even date herewith, relates to griseofulvin-containing compositions suitable for such topical application. We have also found however that fungus diseases of man and animals may be treated by oral or parenteral administration of suitable compositions comprising griseofulvin. This is particularly surprising in respect of those fungus diseases which are skin diseases.

According to this invention therefore we provide compositions suitable for the treatment of fungus diseases of man and animals which comprise griseofulvin as active fungicidal ingredient and pharmaceutical excipients known for the production of formulations suitable for oral or parenteral administration.

The griseofulvin is preferably present in the compositions in such proportion by weight that the proportion by weight of griseofulvin in the formulation to be administered lies between 0.1% and 90%.

Compositions suitable for oral administration are the known pharmaceutical forms for such administration, namely for example tablets, pills, syrups, and aqueous or oily suspensions and the excipients used in the production of these formulations are the excipients well known to the pharmacist's art, as are also the means of formulation.

Suitable compositions may be tablets wherein the griseofulvin is mixed with an inert diluent for example calcium carbonate or lactose in the presence of disintegrating agents for example maize starch and lubricating agents for example magnesium stearate. Aqueous suspensions for oral use may contain griseofulvin in aqueous media in the presence of a non-toxic suspending agent for example sodium carboxymethylcellulose and dispersing agents. Suitable dispersing agents may be for example lecithin or condensation products of ethylene oxide with fatty acids for example polyoxyethylene stearate or with fatty alcohols for example heptadeca-ethyleneoxy-cetanol or with esters or partial esters derived from the fatty acids and hexitols for example polyoxyethylene sorbitol hexa-oleate, or with esters or partial esters derived from the fatty acids and hexitol anhydrides, for example hexitans derived from sorbitol, for example polyoxyethylene sorbitan mono-oleate. Oily suspensions for oral use may be formulated in a vegetable oil for example arachis oil which may contain sweetening agents and preservatives.

For the treatment of animals especially, by oral administration, the griseofulvin may first be incorporated into food premixes and the said premixes then used for incorporation into animal foodstuffs. The said food premixes may comprise griseofulvin in admixture with a diluent or carrier for example talc or lactose and/or other non-toxic and orally-acceptable ingredients.

Compositions suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media.

[Price 3s. 6d.]

The excipients used in these formulations are the excipients well known to the pharmacist's art, as are also the means of formulation.

The sterile aqueous suspensions for parenteral administration may be formulated in the presence of parenterally-acceptable suspending agents and dispersing agents. Suitable suspending agents may be for example sodium carboxymethylcellulose, sodium alginate or polyvinylpyrrolidone and suitable dispersing agents may be lecithin or the ethylene oxide condensation products described above for use as dispersing agents in the preparation of oral aqueous suspensions. Suitable injectable oily preparations may be prepared by dispersing griseofulvin in an oily medium for example a vegetable oil for example arachis oil which is known to be non-toxic and parenterally-acceptable.

The invention is illustrated but not limited by the following examples in which the parts are by weight:—

EXAMPLE 1.

500 parts of griseofulvin are mixed with 70 parts of calcium carbonate and 200 parts of a 10% maize starch paste are added. The mixture is dried and is then passed through a 16-mesh screen. 5 parts of magnesium stearate are added and the granules are compressed to give tablets suitable for administration.

EXAMPLE 2.

A mixture of 1.5 parts of polyglyceryl recinoleate and 0.1 part of sodium carboxymethylcellulose is stirred with 90 parts of distilled water. 10 parts of griseofulvin are then added and the mixture is ball-milled. The stable suspension thus obtained is sterilised and is then suitable for administration by injection.

EXAMPLE 3.

150 parts of griseofulvin in fine powder form are mixed with 500 parts of lactose and 100 parts of maize starch and the mixture is treated with sufficient 10% maize starch paste to give a granular mass. This mixture is passed through a 16-mesh sieve and then dried. 8 parts of magnesium stearate are incorporated in the dried product and the resulting granules are then compressed into tablets suitable for administration.

EXAMPLE 4.

A mixture is formulated from 2 parts of griseofulvin and 98 parts of talc and there is thus obtained a composition suitable for use as a premix for admixture with animal foodstuffs.

EXAMPLE 5.

A mixture is formulated from 5 parts of griseofulvin and 95 parts of lactose and there is thus obtained a composition suitable for use as a premix for admixture with animal foodstuffs.

EXAMPLE 6.

100 parts of griseofulvin in fine powder form is added to a finely ground mixture of 29 parts of icing sugar, 0.6 part of sodium saccharine and 0.05 part of propyl gallate and the mixture is stirred until uniform. The compound powder thus obtained is suspended in 870 parts of arachis oil according to the art, 0.35 part of fruit flavour is added and there is thus obtained an oily dispersion suitable for oral use.

EXAMPLE 7.

A mixture of 10 parts of griseofulvin and 90 parts of arachis oil is ball-milled until substantially all the particles are below 50 microns in diameter. The suspension is then sterilised and is then suitable for administration by injection.

EXAMPLE 8.

142 parts of griseofulvin, 0.5 part of heptadeca-ethylene oxycetanol and 900 parts of water are ball-milled for one hour. 10 parts of medium viscosity sodium carboxymethylcellulose are then added and ball-milling is continued for a further 4 hours until the bulk or mass of the griseofulvin in suspension is 50—60 microns. There is thus obtained a suspension suitable for dilution for oral use for therapeutic purposes for example as a drench for animals.

EXAMPLE 9.

A solution is prepared by dissolving 1.5 parts of methyl *p*-hydroxybenzoate, 0.2 part of propyl *p*-hydroxybenzoate, 2.5 parts of refined soya bean lecithin and 8 parts of polyvinylpyrrolidone in 1000 parts of distilled water. The aqueous vehicle so obtained is sterilised by heating in an autoclave. To the sterile aqueous vehicle so obtained 158 parts of sterile micropulverised griseofulvin are added. The resulting mixture is ball-milled for 15 minutes and there is thus obtained a suspension suitable for parenteral administration for therapeutic purposes.

WHAT WE CLAIM IS:—

1. Compositions suitable for the treatment of fungus diseases of man and animals which comprise griseofulvin as active fungicidal ingredient and pharmaceutical excipients known for the production of formulations suitable for oral or parenteral administration.

2. Compositions as claimed in Claim 1 wherein the griseofulvin is present in such proportion by weight that the proportion by weight of griseofulvin in the formulation to be administered lies between 0.1% and 90%.

3. Compositions as claimed in Claims 1 and 2 which are suitable for oral administration and are in the form of tablets, pills, syrups or aqueous or oily suspensions.

4. Compositions as claimed in Claim 3 wherein the tablets contain griseofulvin in admixture with an inert diluent for example calcium carbonate or lactose in the presence of a disintegrating agent for example maize and a

The excipients used in these formulations are the excipients well known to the pharmacist's art, as are also the means of formulation.

The sterile aqueous suspensions for parenteral administration may be formulated in the presence of parenterally-acceptable suspending agents and dispersing agents. Suitable suspending agents may be for example sodium carboxymethylcellulose, sodium alginate or polyvinylpyrrolidone and suitable dispersing agents may be lecithin or the ethylene oxide condensation products described above for use as dispersing agents in the preparation of oral aqueous suspensions. Suitable injectable oily preparations may be prepared by dispersing griseofulvin in an oily medium for example a vegetable oil for example arachis oil which is known to be non-toxic and parenterally-acceptable.

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EXAMPLE 1.

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EXAMPLE 2.

A mixture of 1.5 parts of polyglyceryl recinoleate and 0.1 part of sodium carboxymethylcellulose is stirred with 90 parts of distilled water. 10 parts of griseofulvin are then added and the mixture is ball-milled. The stable suspension thus obtained is sterilised and is then suitable for administration by injection.

EXAMPLE 3.

150 parts of griseofulvin in fine powder form are mixed with 500 parts of lactose and 100 parts of maize starch and the mixture is treated with sufficient 10% maize starch paste to give a granular mass. This mixture is passed through a 16-mesh sieve and then dried. 8 parts of magnesium stearate are incorporated in the dried product and the resulting granules are then compressed into tablets suitable for administration.

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2. Compositions as claimed in Claim 1 wherein the griseofulvin is present in such proportion by weight that the proportion by weight of griseofulvin in the formulation to be administered lies between 0.1% and 90%.

3. Compositions as claimed in Claims 1 and 2 which are suitable for oral administration and are in the form of tablets, pills, syrups or aqueous or oily suspensions.

4. Compositions as claimed in Claim 3 wherein the tablets contain griseofulvin in admixture with an inert diluent for example calcium carbonate or lactose in the presence of a disintegrating agent for example maize and a

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lubricating agent for example magnesium stearate.

5. Compositions as claimed in Claim 3 wherein the aqueous suspensions contain griseofulvin in aqueous media in the presence of a non-toxic suspending agent for example sodium carboxymethylcellulose and a dispersing agent.

6. Compositions as claimed in Claim 3 wherein the oily suspensions contain griseofulvin formulated in a vegetable oil for example arachis oil.

7. Compositions as claimed in Claims 1 and 2 which are suitable for oral administration and are in the form of food premixes suitable for incorporation into animal foodstuffs.

8. Compositions as claimed in Claim 7 wherein the food premix comprises griseofulvin in admixture with a diluent or carrier for example talc or lactose and/or other non-toxic and orally acceptable ingredients.

9. Compositions as claimed in Claims 1 and 2 which are suitable for parenteral administration and are in the form of sterile suspensions in aqueous or oily media.

10. Compositions as claimed in Claim 9 which are sterile aqueous suspensions wherein the griseofulvin is formulated in the presence of parenterally-acceptable suspending agents and dispersing agents.

11. Compositions as claimed in Claim 10 wherein the suspending agent is sodium carboxymethylcellulose, sodium alginate or polyvinylpyrrolidone.

12. Compositions as claimed in Claims 5, 10 and 11 wherein the dispersing agent is lecithin or a condensation product of ethylene oxide with a fatty acid for example polyoxyethylene stearate or with a fatty alcohol for example heptadeca-ethyleneoxycetanol or with an ester or a partial ester derived from a fatty acid and a hexitol for example polyoxyethylene sorbitol hexaoleate or with an ester or a partial ester derived from a fatty acid and a hexitol anhydride for example polyoxyethylene sorbitan mono-oleate.

13. Compositions as claimed in Claim 9 which are sterile oily suspensions wherein the griseofulvin is formulated in the presence of a vegetable oil for example arachis oil.

14. Compositions as claimed in Claims 1—13 as hereinebefore particularly described and especially with reference to the foregoing examples.

WALTER SCOTT,
Agents for the Applicants.

PROVISIONAL SPECIFICATION

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Furthermore many important fungus diseases of man and animals are skin diseases, for example ringworm and athlete's foot, and these are commonly treated by topical application of medicaments in the form of ointment and the like. Our copending Application No. 28904/56 (Serial No. 810,377), of even date herewith, relates to griseofulvin-containing compositions suitable for such topical application. We have also found however that fungus diseases of man and animals may be treated by oral or parenteral administration of suitable compositions comprising griseofulvin. This is particularly surprising in respect of those fungus diseases which are skin diseases.

According to this invention therefore we provide new compositions suitable for the treatment of fungus diseases of man and animals which comprise griseofulvin as active fungicidal ingredient and pharmaceutical excipients known for the production of formulations suitable for oral or parenteral administration.

The griseofulvin is preferably present in the compositions in such proportion by weight that the proportion by weight of griseofulvin in the formulation used lies between 0.1% and 50%.

Compositions suitable for oral administration are the known pharmaceutical forms for such administration, namely for example tablets, pills and syrups, and the excipients used in the production of these formulations are the excipients well known to the pharmacist's art, as are also the means of formulation.

For the treatment of animals especially, by oral administration, the griseofulvin may be incorporated in nutrient materials, foodstuffs and mixtures of foodstuffs for example.

Compositions suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media. The excipients used in these formulations are the excipients well known to the pharmacist's art, as are also the means of formulation.

The invention is illustrated but not limited by the following examples in which the parts are by weight:—

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Agent for the Applicants.

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