

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Fungicidal Compositions

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 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 treatment of fungus diseases of man and animals.

We have found that compositions comprising griseofulvin and certain bland high-boiling fluids, especially such as aid absorption into the skin, are useful in the treatment, by topical application, of fungus diseases of man and animals, such fungus diseases for example as athlete's foot and ringworm.

According to the invention we provide therefore new fungicidal compositions which comprise griseofulvin and a bland high-boiling fluid, as hereinafter defined, the griseofulvin being preferably present in such proportion by weight that the proportion by weight of griseofulvin in the composition applied lies between 0.1% and 50%.

By the word "bland" we mean such fluids as are mild and inoffensive to the skin of man and animals, non-toxic, non-corrosive and non-irritant. By "high-boiling" we mean fluids of such boiling point as will not rapidly evaporate when applied to the skin. Preferably the fluids used are of boiling point above 150° C. The term "fluid" is used to include, besides liquids, also semi-solid materials, for example greases, pastes, waxes and the like.

The preferred fluids to be used in the com-

positions of the invention are those which are solvents for griseofulvin and which further possess the property of being readily absorbed by the skin.

It is to be understood that the expression "bland high-boiling fluid" does not include any of the solvents, cyclohexanone, methylcyclohexanone, furfural or water-miscible N-alkyl amides of aliphatic acids or mixtures of the said solvents.

Suitable fluids are those bland, high-boiling fluids of animal and vegetable origin and also certain synthetic fluids. There may be used for example lanoline, castor oil, arachis oil, 2:2-dimethylpropane-1:3-diol, dimethylsulphoxide and polyethyleneglycol-400. Generally speaking vegetable oils are preferred and of these we have found arachis oil to be particularly suitable.

As said the proportion by weight of griseofulvin in the formulation applied should be between 0.1% and 50%. It is not essential that the whole of the griseofulvin should be dissolved in the fluid. Thus compositions which are essentially suspensions of griseofulvin in solutions of griseofulvin in a suitable fluid may be used.

The compositions of the invention are, as said, applied topically to the site of the fungus infection in man or animals. They may be applied as such or they may be applied in the form for example of creams, jellies, ointments, lotions, paints and collodions in which the composition of the invention is incorporated with suitable further ingredients suitable to the production of the desired administrable form. The formulation of said creams, jellies, ointments, lotions, paints and collodions may be accomplished by means well known to the pharmacist's art and any of the known means are applicable.

Thus suitable creams may be formulated by admixture of the griseofulvin and bland high-

[Price 3s. 6d.]



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boiling fluid for example arachis oil or castor oil, with fatty ingredients such as cetostearyl alcohol or stearic acid, and water in the presence of an emulsifying agent for example sodium lauryl sulphate, Cetomacrogol 1000 B.P.C. or triethanolamine. Ointment formulations may be prepared by admixture of the griseofulvin and bland high-boiling fluid for example lanoline with a suitable hydrocarbon material for example a mixture of hard and/or soft paraffin or by admixture of the griseofulvin with a mixture of polyethyleneglycol-400 and polyethyleneglycol-4000. However it is preferred to use compositions from which substantial amounts of water are absent since there is a tendency for maceration of the skin with consequent delayed healing to occur when such formulations as contain appreciable amounts of water are used.

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

EXAMPLE 1

1.05 parts of griseofulvin, 85 parts of 2:2-dimethylpropane-1:3-diol, 7 parts propylene glycol and 12 parts of glycerol are mixed together to provide a mixture suitable for topical application.

EXAMPLE 2

1 part of griseofulvin and 99 parts of dimethylsulphoxide are mixed together to provide a mixture suitable for topical application.

EXAMPLE 3

1 part of griseofulvin and 99 parts of polyethyleneglycol-400 are mixed together to provide a mixture suitable for topical application.

EXAMPLE 4

1 part of griseofulvin and 99 parts of arachis oil are mixed together to provide a mixture suitable for topical application.

EXAMPLE 5

0.2 part of griseofulvin as a fine powder is stirred at 10° C. for 10 minutes with 12 parts of arachis oil and 10 parts of cetostearyl alcohol. To the mixture is added one part of sodium lauryl sulphate in solution in 76.8 parts of water at 70° C. The mixture is stirred and homogenised and cooled and there is thus obtained a cream suitable for topical application.

EXAMPLE 6

0.5 part of griseofulvin in fine powder form is stirred at 70° C. for 10 minutes with 35 parts of arachis oil, 12 parts of cetostearyl alcohol and 2 parts of Cetomacrogol-1000 B.P.C. 50.5 parts of water at 70° C. are then added and the mixture is stirred and homogenised and cooled. There is thus obtained a cream suitable for topical application.

EXAMPLE 7

1.0 part of griseofulvin in fine powder form is added to a mixture at 70° C. of 15 parts of stearic acid and 17 parts of castor oil and the resultant mixture is stirred for 10 minutes. To this mixture there is added a solution of one part of triethanolamine in 66 parts of water at 70° C. The mixture is stirred and homogenised and cooled and there is thus obtained a cream suitable for topical application.

EXAMPLE 8

One part of griseofulvin in fine powder form is added to a molten mixture of 50 parts of arachis oil, 20 parts of soft paraffin, 20 parts of hard paraffin and 9 parts of lanoline and the resultant mixture is stirred for 10 minutes at 70° C. It is then cooled with stirring and there is thus obtained an ointment suitable for topical application.

EXAMPLE 9

0.5 part of griseofulvin in fine powder form is added to a solution of 3 parts of sodium alginate and 3 parts of glycerol in 93.5 parts of water at 50° C. and the mixture is stirred until uniform and is then cooled to give a jelly suitable for topical application.

EXAMPLE 10

0.4 part of tragacanth suspended in a mixture of 5 parts of ethyl alcohol and 10 parts of glycerol is added to 80 parts of water and the mixture is allowed to stand with occasional stirring until a uniform preparation results. One part of griseofulvin in fine powder form is then added with stirring and water is added to give a total of 100 parts. There is thus obtained a lotion suitable for application to the skin.

EXAMPLE 11

5 parts of pyroxylin are dissolved in 50 parts of acetone and 4 parts of castor oil and 10 parts of β -ethoxyethanol are added. One part of griseofulvin in fine powder form is suspended in 30 parts of acetone and the suspension is added to the said solution with constant stirring. There is thus obtained a collodion suitable for application to the skin.

EXAMPLE 12

600 parts of polyethyleneglycol-4000, 885 parts of polyethyleneglycol-400 and 14 parts of griseofulvin are heated together with stirring at 60° C. until a homogeneous solution is obtained. The solution is stirred while it is allowed to cool to normal temperature and there is thus obtained an ointment suitable for topical application for therapeutic purposes.

WHAT WE CLAIM IS:—

1. New fungicidal compositions which comprise griseofulvin and a bland high-boiling fluid as hereinbefore defined.
2. Compositions as claimed in Claim 1 wherein the griseofulvin is present in such pro-

- boiling fluid for example arachis oil or castor oil, with fatty ingredients such as cetostearyl alcohol or stearic acid, and water in the presence of an emulsifying agent for example sodium lauryl sulphate, Cetomacrogol 1000 B.P.C. or triethanolamine. Ointment formulations may be prepared by admixture of the griseofulvin and bland high-boiling fluid for example lanoline with a suitable hydrocarbon material for example a mixture of hard and/or soft paraffin or by admixture of the griseofulvin with a mixture of polyethyleneglycol-400 and polyethyleneglycol-4000. However it is preferred to use compositions from which substantial amounts of water are absent since there is a tendency for maceration of the skin with consequent delayed healing to occur when such formulations as contain appreciable amounts of water are used.
- The invention is illustrated but not limited by the following examples in which the parts are by weight:—
- EXAMPLE 1**
- 1.05 parts of griseofulvin, 85 parts of 2:2-dimethylpropane-1:3-diol, 7 parts propylene glycol and 12 parts of glycerol are mixed together to provide a mixture suitable for topical application.
- EXAMPLE 2**
- 1 part of griseofulvin and 99 parts of dimethylsulphoxide are mixed together to provide a mixture suitable for topical application.
- EXAMPLE 3**
- 1 part of griseofulvin and 99 parts of polyethyleneglycol-400 are mixed together to provide a mixture suitable for topical application.
- EXAMPLE 4**
- 1 part of griseofulvin and 99 parts of arachis oil are mixed together to provide a mixture suitable for topical application.
- EXAMPLE 5**
- 0.2 part of griseofulvin as a fine powder is stirred at 10° C. for 10 minutes with 12 parts of arachis oil and 10 parts of cetostearyl alcohol. To the mixture is added one part of sodium lauryl sulphate in solution in 76.8 parts of water at 70° C. The mixture is stirred and homogenised and cooled and there is thus obtained a cream suitable for topical application.
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- 0.5 part of griseofulvin in fine powder form is stirred at 70° C. for 10 minutes with 35 parts of arachis oil, 12 parts of cetostearyl alcohol and 2 parts of Cetomacrogol-1000 B.P.C. 50.5 parts of water at 70° C. are then added and the mixture is stirred and homogenised and cooled. There is thus obtained a cream suitable for topical application.
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1. New fungicidal compositions which comprise griseofulvin and a bland high-boiling fluid as hereinbefore defined.
 2. Compositions as claimed in Claim 1 wherein the griseofulvin is present in such pro-



- portion by weight that the proportion by weight of griseofulvin in the composition lies between 0.1% and 50%.
3. Compositions as claimed in Claims 1 and 2 wherein the fluid has a boiling point above 150° C.
4. Compositions as claimed in Claims 1—3 wherein the fluid is a solvent for griseofulvin.
5. Compositions as claimed in Claims 1—4 wherein the fluid is one readily absorbed by the skin.
6. Compositions as claimed in Claims 1—5 wherein the fluid is of animal or vegetable origin.
7. Compositions as claimed in Claims 1—5 wherein the fluid is of synthetic origin.
8. Compositions as claimed in Claims 1—6 wherein the fluid is selected from lanoline, castor oil and arachis oil.
9. Compositions as claimed in Claims 1—5 and 7 wherein the fluid is selected from polyethyleneglycol-400, 2:2-dimethylpropane-1:3-diol and dimethylsulphoxide.
10. Compositions as claimed in Claims 1—9 wherein the griseofulvin is in part dissolved and in part suspended in the fluid.
11. Compositions as claimed in Claims 1—10 which are in the form of creams, jellies, ointments, lotions, paints or collodions.
12. Compositions as claimed in Claims 1—11 wherein there are present fatty ingredients additional to the bland high-boiling fluid.
13. Compositions as claimed in Claim 12 wherein the fatty ingredient is selected from cetostearyl alcohol and stearic acid.
14. Compositions as claimed in Claims 1—13 wherein no substantial amount of water is present.
15. Compositions comprising griseofulvin and a vegetable oil.
16. Compositions comprising griseofulvin and arachis oil.
17. Compositions which comprise solutions of griseofulvin in arachis oil.
18. Compositions which comprise suspensions of griseofulvin in solutions of griseofulvin in arachis oil.
19. Compositions, claimed in Claims 1—18, as hereinbefore particularly described and especially with reference to the foregoing examples.

WALTER SCOTT,
Agent for the Applicants.

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PROVISIONAL SPECIFICATION

Fungicidal Compositions

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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 treatment of fungus diseases of man and animals.

We have found that compositions comprising griseofulvin and certain bland high-boiling fluids, especially such as aid absorption into the skin, are useful in the treatment, by topical application, of fungus diseases of man and animals, such fungus diseases for example as athlete's foot and ringworm.

According to the invention we provide therefore new fungicidal compositions which comprise griseofulvin and a bland high-boiling fluid the griseofulvin being present in such proportions by weight that the proportion by weight of griseofulvin in the formulation applied lies between 0.1% and 50%.

As bland high-boiling fluids there may be used for example vegetable oils, for example arachis oil and certain synthetic bland high-boiling fluids, for example 2:2-dimethylpropane-1:3-diol, dimethylsulphoxide and polyethyleneglycol-400. The preferred bland high-boiling fluids are the naturally occurring vegetable oils and of these arachis oil is preferred.

The compositions of the invention are, as said, applied topically to the site of the fungus infection in man or animals. They may be applied as such or they may be applied in the form for example of creams, ointments, lotions, paints and collodions in which the composition of the invention is incorporated with suitable further ingredients suitable to the production of the desired administrable form. The formulation of said creams, ointments, lotions, paints and collodions may be accomplished by means well known to the pharmacist's art and any of the known means are applicable.

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

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EXAMPLE 2

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EXAMPLE 3

1 part of griseofulvin and 99 parts of poly-



ethyleneglycol-400 are mixed together to provide a mixture suitable for topical application. oil are mixed together to provide a mixture suitable for topical application. 5

EXAMPLE 4

1 part of griseofulvin and 99 parts of arachis

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