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(19)



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(54) IMPROVED INDOMETHACIN SUPPOSITORIES

(71) We, MERCK & CO INC, a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, 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 indomethacin and is more particularly concerned with suppositories containing indomethacin in crystalline form, glycerin and a crystalline nucleating agent in a polyethylene glycol base, and their preparation. The polyethylene glycol bases included herein are highly desirable due to their solubility in water and in the secretions of mucous membranes.

The literature teaches the preparation of indomethacin suppositories in a polyethylene glycol base which includes 4—12% by weight of glycerol (see U.S. Patent No. 3,644,630 and U.K. Patent No. 1,284,192).

It is known that in the preparation of suppositories, discoloration, esterification and other undesirable conditions may result which affect the chemical and physical stability of the suppositories.

A continuous search has been carried out for a process for preparing indomethacin suppositories that possess both chemical and physical stability, and the discovery on which this invention is based in that the addition of from 4—12%, by weight of the suppository, of glycerol U.S.P. and from 1.0—4.5%, by weight of the suppository, of a pharmaceutically acceptable crystalline material, which acts as nucleating agent, to a molten polyethylene glycol base containing dissolved indomethacin, results in an unexpected enhanced stable condition.

To practise this invention, a molten solution of indomethacin and polyethylene glycol is prepared, to which are added from 1.0—4.5% by weight of the suppository of a pharmaceutically acceptable crystalline material, which acts as a nucleating agent, and from 4—12% by weight of the suppository of glycerol. This product may be prepared at those temperatures which will provide a molten state. The mass is then sub-divided into suppository doses and allowed to congeal by lowering the temperature of the system. It is preferred to congeal at room temperature. The indomethacin contained in the suppository crystallizes in the matrix within a short period of time after congealing commences. If the nucleating agent is not present, then excessive time is required for crystallization to occur. The condition can result in the preparation of suppositories which possess undesirable conditions such as esterification and discolouration. In accordance with the present invention, such suppositories are administered to non-human animals suffering from a condition exhibiting at least one of the symptoms of pain, fever and inflammation in order to treat the said condition.

The polyethylene glycol base may be made from any suitable pharmaceutical grade polyethylene glycol or mixtures thereof of various molecular weights which are used to prepare supositories that are soluble in water and in the secretions of mucous membranes. Representative polyethylene glycol bases are polyethylene glycol 1000, 1540, 4000 and 6000. The selection of the exact composition of the base will, of course, depend on the properties desired in the suppository, such as solubility, congealing temperature and size. The preferred bases are those prepared from polyethylene glycol 4000 and polyethylene glycol 6000. The amount of the base is not critical and will depend on the overall size of the suppository, the desired use, and the dosage of indomethacin in each

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suppository. For example, the amount of base can vary from 50% to 95% by weight of the suppository.

Representative nucleating agents that can be used in the practice of the invention are alkali metal halides such as sodium chloride and potassium chloride, calcium chloride, lactose and sucrose. Of particular reference is sodium chloride. The congealing temperature will, of course, depend on the composition of the base.

Indomethacin is a drug which has anti-inflammatory, analgesic and anti-pyretic properties. The chemical name is 1 - (p - chlorobenzoyl) - 5 - methoxy - 2 - methyl-indole - 3 - acetic acid. Seen United States Patent No. 3,161,654.

With respect to the dose level, it should be noted, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, time of administration, rate of excretion, and the severity of the disease undergoing therapy.

The following examples are given to illustrate the invention and are not intended to be a limitation thereof.

Ingredients	Percent by weight			
Polyethylene glycol 4000	88.6	84.6	81.00	77.6
Polyethylene glycol 6000	—	—	—	7.8
Sodium chloride	3.5	3.45	3.45	3.4
Glycerol U.S.P.	4.4	8.5	12.1	7.8
Indomethacin	3.5	3.45	3.45	3.4

The polyethylene glycols are heated to 65° C. and upon melting, indomethacin is added and dissolved. Sodium chloride is then suspended in the molten mass with stirring. The temperature of the mass is reduced to 55—60°C. and maintained for 10—15 minutes while glycerol is added. The mass is then sub-divided into suppositories containing the desired amount of drug and congealed at room temperature. Further storage at 5°C. and ambient temperature yields an elegant white opaque suppository.

WHAT WE CLAIM IS:—

1. A suppository comprising a dosage unit amount of crystalline indomethacin in a base comprised of a polyethylene glycol or a mixture of polyethylene glycols, from 1.0—4.5% by weight of a pharmaceutically acceptable crystalline material, which acts as a nucleating agent, and from 4—12% by weight of glycerol.

2. A suppository according to Claim 2, in which the dosage unit amount of indomethacin ranges from 40—110 mg.

3. A suppository according to Claim 2, in which the dosage unit amount of indomethacin is 50 mg.

4. A suppository according to any one of Claims 1—3, in which the polyethylene glycol is polyethylene glycol 4000 or polyethylene glycol 6000 or a mixture thereof and the nucleating agent is an alkali metal halide, lactose, calcium chloride or sucrose.

5. A suppository according to Claim 4, in which the polyethylene glycol base is a mixture of polyethylene glycol 4000 and polyethylene glycol 6000, and the nucleating agent is sodium chloride.

6. A suppository according to Claim 1, substantially as hereinbefore described in any one of the Examples.

7. A method of preparing a suppository that comprises adding from 4—12% by weight of glycerol to a molten polyethylene glycol base which contains indomethacin and 1.0—4% by weight of a pharmaceutically acceptable crystalline material, which acts as a nucleating agent, allowing the molten mixture to congeal and subdividing it into suppositories containing a dosage unit amount of crystalline indomethacin.

8. A method according to Claim 7, in which the molten polyethylene glycol base is prepared at about 65°C. and allowed to congeal at about room temperature.

9. A method according to Claim 7, in which the polyethylene glycol base is polyethylene glycol 4000 or polyethylene glycol 6000 or a mixture thereof, and the nucleating agent is an alkali metal halide, calcium chloride, lactose or sucrose.

10. A method according to Claim 9, in which the base is a mixture of polyethylene glycol 4000 and polyethylene glycol 6000, and the nucleating agent is sodium chloride.

11. A method according to Claim 7, substantially as hereinbefore described in any one of the foregoing Examples.

12. A method of treating a non-human

suppository. For example, the amount of base can vary from 50% to 95% by weight of the suppository.

Representative nucleating agents that can be used in the practice of the invention are alkali metal halides such as sodium chloride and potassium chloride, calcium chloride, lactose and sucrose. Of particular reference is sodium chloride. The congealing temperature will, of course, depend on the composition of the base.

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With respect to the dose level, it should be noted, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, time of administration, rate of excretion, and the severity of the disease undergoing therapy.

The following examples are given to illustrate the invention and are not intended to be a limitation thereof.

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The polyethylene glycols are heated to 65° C. and upon melting, indomethacin is added and dissolved. Sodium chloride is then suspended in the molten mass with stirring. The temperature of the mass is reduced to 55—60°C. and maintained for 10—15 minutes while glycerol is added. The mass is then sub-divided into suppositories containing the desired amount of drug and congealed at room temperature. Further storage at 5°C. and ambient temperature yields an elegant white opaque suppository.

WHAT WE CLAIM IS:—

1. A suppository comprising a dosage unit amount of crystalline indomethacin in a base comprised of a polyethylene glycol or a mixture of polyethylene glycols, from 1.0—4.5% by weight of a pharmaceutically acceptable crystalline material, which acts as a nucleating agent, and from 4—12% by weight of glycerol.

2. A suppository according to Claim 2, in which the dosage unit amount of indomethacin ranges from 40—110 mg.

3. A suppository according to Claim 2, in which the dosage unit amount of indomethacin is 50 mg.

4. A suppository according to any one of Claims 1—3, in which the polyethylene glycol is polyethylene glycol 4000 or polyethylene glycol 6000 or a mixture thereof and the nucleating agent is an alkali metal halide, lactose, calcium chloride or sucrose.

5. A suppository according to Claim 4, in which the polyethylene glycol base is a mixture of polyethylene glycol 4000 and polyethylene glycol 6000, and the nucleating agent is sodium chloride.

6. A suppository according to Claim 1, substantially as hereinbefore described in any one of the Examples.

7. A method of preparing a suppository that comprises adding from 4—12% by weight of glycerol to a molten polyethylene glycol base which contains indomethacin and 1.0—4% by weight of a pharmaceutically acceptable crystalline material, which acts as a nucleating agent, allowing the molten mixture to congeal and subdividing it into suppositories containing a dosage unit amount of crystalline indomethacin.

8. A method according to Claim 7, in which the molten polyethylene glycol base is prepared at about 65°C. and allowed to congeal at about room temperature.

9. A method according to Claim 7, in which the polyethylene glycol base is polyethylene glycol 4000 or polyethylene glycol 6000 or a mixture thereof, and the nucleating agent is an alkali metal halide, calcium chloride, lactose or sucrose.

10. A method according to Claim 9, in which the base is a mixture of polyethylene glycol 4000 and polyethylene glycol 6000, and the nucleating agent is sodium chloride.

11. A method according to Claim 7, substantially as hereinbefore described in any one of the foregoing Examples.

12. A method of treating a non-human

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animal suffering from a condition exhibiting at least one of the symptoms of pain, fever and inflammation which comprises the administration of a suppository according to any one of Claims 1—6.

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