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(54) 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:—

Suppositories prepared from a polyethylene glycol base are highly desirable since these bases are especially soluble in water and in the secretions of the mucous membranes.

Indomethacin is a drug which has anti-inflammatory, analgesic and anti-pyretic properties. The chemical name is 1 - (*p* - chlorobenzoyl) - 5 - methoxy - 2 - methylindole - 3 - acetic acid and the compound is prepared as disclosed in United States Patent No. 3 161 654 and UK Patent No. 997 638. It is desirable to prepare suppositories of indomethacin which have this polyethylene glycol base. This drug, however, is soluble in polyethylene glycols and therefore dissolves readily in the molten base. Upon congealing, the indomethacin remains in solution in the solid base. This system is therefore physically in an unstable condition which may readily change to a more stable or less stable condition. Since indomethacin is molecularly dispersed in the base, discoloration and esterification often result. Further, a mottled appearance occurs from extremely slow crystallization of the drug within the matrix, and the onset of this crystallization is unpredictable.

It has now been found that by the addition of from about 4—12% by weight of glycerol U.S.P. to a molten polyethylene glycol base containing dissolved indomethacin, an unexpected stable condition results. The associated discoloration and esterification no longer results and crystallization of the drug in this environment gives an opaque product free from any mottled appearance. Further, the indomethacin of the suppository is both physically stable and chemically less reactive after crystallization in the matrix. This results in a product which is as biologically available as that dispersed at the molecular level.

The present invention provides a suppository comprising a dosage unit amount of indomethacin in a base comprising a polyethylene glycol or a mixture of polyethylene glycols and from about 4—12% by weight of glycerol, based on the total weight of indomethacin, polyethylene glycol and glycerol. In accordance with the present invention, such suppositories are prepared by adding from about 4—12% by weight of glycerol, based on the total weight of indomethacin, polyethylene glycol and glycerol, to a molten polyethylene glycol base containing indomethacin, dividing up the molten mixture and allowing it to congeal. The molten solution may be prepared in the usual manner at a raised temperature, preferably about 65°C, which will provide a molten state. The mass is then divided into suppository doses and allowed to congeal by lowering the temperature of the system. It is preferred to congeal at about 5°C, although cooling only down to room temperature is quite convenient. The indomethacin contained in the suppository crystallizes in the matrix within a short period of time after congealing commences.

The polyethylene glycol base may be made from any suitable polyethylene glycol or mixture thereof of various molecular weights that are used to prepare suppositories that are soluble in water and in the secretions of mucous membranes. The selection of the composition of the base will, of course, depend on the properties desired in the suppository, such as solubility, congealing temperature and acidity. The preferred bases are those prepared from polyethylene glycol 4000 and poly-

[*Price 25p*]

ethylene glycol 6000. The amount of the base used is not a critical feature and will depend on the overall size of the suppository, the desired use, and the dosage of indomethacin in each suppository. The congealing temperature will, of course, depend on the composition of the base.

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

Ingredients	Percent by Weight			
Polyethylene glycol 4000	88.6	84.6	81.0	77.6
Polyethylene glycol 6000	—	—	—	7.8
Glycerol U.S.P.	4.4	8.5	12.1	7.8
Indomethacin	7.0	6.9	6.9	6.8

The polyethylene glycols are heated to 65° C. and upon melting, the glycerin is added. The indomethacin is dissolved in the molten mass with stirring. The mass is then subdivided into suppositories containing the desired amount of drug and congealed.

WHAT WE CLAIM IS:—

1. A suppository comprising a dosage unit amount of indomethacin in a base comprising a polyethylene glycol or a mixture of polyethylene glycols and from about 4—12% by weight of glycerol, based on the total weight of indomethacin, polyethylene glycol and glycerol.

2. A suppository as claimed in claim 1 in which the polyethylene glycol is polyethylene glycol 4000 or polyethylene glycol 6000.

3. A method for preparing suppositories as claimed in claim 1 that comprises adding from about 4—12% by weight of glycerol, based on the total weight of indomethacin, polyethylene glycol and glycerol, to a molten polyethylene glycol base containing indomethacin, dividing up the molten mixture and allowing it to congeal.

4. A method as claimed in claim 3 in which the molten base is prepared at about 65°C and allowed to congeal at about 5°C.

5. A method as claimed in claim 3 or 4 in which the polyethylene glycol is polyethylene glycol 4000 or polyethylene glycol 6000.

6. A method as claimed in claim 3 substantially as hereinbefore described in any one of the foregoing Examples.

7. Suppositories prepared by a method as claimed in any one of claims 3—6.

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