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(19)



(54) IMPROVEMENTS IN OR RELATING TO PHARMACEUTICAL PREPARATIONS

(71) We, CIBA-GEIGY A.G, a body corporate organised according to the laws of Switzerland, of 4002 Basle, Switzerland, 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:—

The present invention relates to pharmaceutical preparations having antiphlogistic, analgesic and antipyretic activity which are suitable for the treatment of rheumatic, arthritic and other inflammatory diseases and conditions.

4 - Butyl - 1 - (p - hydroxyphenyl) - 2 - phenyl - 3,5 - pyrazolidinedione, which in the following is referred to throughout as oxyphenbutazone (International non-proprietary name, INN), has proved very valuable as an active substance for the treatment of inflammatory and swelling conditions. In certain cases, however, the use of oxyphenbutazone is accompanied by undesirable secondary effects, such as the formation of oedemas, giddiness, vomiting, diarrhoea, and activation of gastric ulcers to the extent that haemorrhages occur, so that in individual cases the daily dosage had to be reduced below the level at which a positive effect is ensured. It would, therefore, be very desirable if the possibility were found of using oxyphenbutazone in a therapeutically effective dosage with, at the same time, a minimum of secondary effects.

Surprisingly, it has now been found that p-hydroxyacetanilide, referred to throughout in the following as paracetamol (INN), intensifies the therapeutically desired effects of oxyphenbutazone in the sense of a synergism, whilst, on the other hand, there tends to occur a reduction in toxicity and at most a summative ulcerogenic activity. It is on these findings that the pharmaceutical preparations according to the invention are based.

The present invention provides a pharmaceutical composition comprising oxyphenbutazone and paracetamol in combination with a pharmaceutically acceptable diluent or carrier therefor, there being present in said composition from 1 to 5, preferably 2 to 4, parts by weight of paracetamol per part by weight of oxyphenbutazone and, optionally, further additives commonly used for the production of pharmaceutical dosage units for oral or rectal administration.

The use of the pharmaceutical preparations according to the invention renders possible, depending on the dosage, the elimination to a very substantial degree of secondary effects, and/or the attainment of a more intensive therapeutic effect. The preparations according to the invention can be used for the treatment of the same inflammatory and swelling conditions for which oxyphenbutazone alone has already been used, and, in addition, in cases requiring a stronger analgesic action, e.g. for the treatment of pains resulting from inflammations.

The reciprocal synergistic intensification of the analgesic and antiphlogistic effectiveness of oxyphenbutazone and of paracetamol in the proportions according to the invention can be determined, for example, in the "writhing test" described by E. Siegmund, R. Cadmus and G. Lu, Proc. Soc. Exp. Biol. Med. *95*, 729 (1957). In this test the amount, orally administered, of paracetamol and oxyphenbutazone individually and in combination required to effect a 50% prevention of the syndome produced in mice by the intraperitoneal injection of 2 - phenyl - 1,4 - benzoquinone is measured.

Finally, a certain potentiation of the antipyretic activity can also be verified.

Suitable dosage units for oral administration are, e.g. tablets, coated tablets (tablets with a compressed coating), dragées and capsules, containing 25—150 mg, preferably 50—125 mg of oxyphenbutazone and 50—500 mg, preferably 100—250 mg of paracetamol, whereby the proportions of the two components are always to be within the above given range. Suppositories and capsules for rectal administration contain 50—250 mg, prefer-

ably 100—250 mg of oxyphenbutazone and 100—500 mg, preferably 200—500 mg of paracetamol, whereby the above given quantity proportions are to be adhered to. The dosage units are administered one to three times daily, the number corresponding to a daily dosage of 100 mg to 500 mg of oxyphenbutazone and the same to fivefold, preferably the double to fourfold amount, of paracetamol for adult patients, with reduced dosages for children depending on age and body weight.

In dosage units for oral administration, the content of the two compounds together used as active substances is between 20% and 90% by weight. Tablets or dragée-cores are produced by combining the active substances, e.g. with solid pulverulent carriers such as milk sugar (lactose), saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives, gelatine or polyvinylpyrrolidone, optionally with the addition of lubricants such as magnesium or calcium stearate, or polyethylene glycols, as well as with highly dispersed silicic acid. Dragée-cores are thereupon coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or mixtures of solvents. Dyestuffs may be added to these coatings, e.g. for identification of the various dosages of active substance. Furthermore, coated tablets can also be produced, analogously to the homogeneous tablets, by firstly, however, preparing tablet-cores containing only one active substance component, and pressing around these cores a coating containing the second active substance component, preferably paracetamol, together with the same or similar carriers and lubricants. Further suitable dosage units for oral administration are hard gelatine capsules, as well as soft closed capsules made from gelatine, and a softener such as glycerin. The hard gelatine capsules contain the active substances preferably as a granulate in admixture with lubricants such as talcum or magnesium stearate and, optionally, stabilisers such as sodium metabisulphite ($Na_2S_2O_5$), or ascorbic acid. In soft capsules, the active substances are preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, whereby likewise stabilisers may be added.

Suitable dosage units for rectal administration are, e.g. suppositories consisting of a combination of the active substances with a suppository foundation substance based on natural or synthetic triglycerides of a suitable melting point (e.g. cocoa butter) or polyethylene glycols; and gelatine rectal capsules containing a combination of the active substance with polyethylene glycols.

The following examples further illustrate the production of a number of typical dosage units, without in any way limiting the scope of the invention. The oxyphenbutazone is preferably used in the form of its monohydrate (decomposition around 76°C with the elimination of water). The monohydrate is obtained in crystalline form if water is added to the acetonic solution of the anhydrous compound.

Example 1

a) Tablet cores are prepared by homogeneously mixing together 7,500 kg of oxyphenbutazone, 1,600 kg of lactose, 1,500 kg of dried maize starch, 0.300 kg of highly dispersed silicic acid, and 0.500 kg of polyvinylpyrrolidone; and the mixture is then moistened and kneaded, with the addition of a sufficient amount of an alcohol (96% by weight)/water mixture (1:1) to obtain a granulatable mass. This is granulated with a granulator, the moist granulate dried to the extent of a relative moisture content of 30—40%, and the dried granulate crushed through a sieve by means of a vibrating granulator. The crushed granulate is homogeneously mixed with 0.500 kg of talcum and 0.100 kg of magnesium stearate, and the obtained mixture pressed to form 100,000 tablet cores each weighing 120 mg.

b) The outer coating is produced by first homogeneously mixing 30,000 kg of paracetamol having a mean particle-size not exceeding 10 μm, 7,000 kg of mannitol, 1,650 kg of dried maize starch and 0.600 kg of polyvinylpyrrolidone; and then granulating the obtained mixture after it has been moistened with an alcohol (96% by weight)/water mixture (1:1) and kneaded until the right condition for granulating has been obtained. The moist granulate is dried to give a relative moisture content of 30%, and then crushed through a sieve by means of a vibrating granulator. The crushed granulate is homogeneously mixed with 0.600 kg of talcum, 0.100 kg of magnesium stearate and 0.050 kg of highly dispersed silicic acid; and the thus obtained mixture compressed around the tablet cores obtained according to a).

In this manner are obtained 100,000 tablets each weighing 520 mg, and each containing 75 mg of oxyphenbutazone and 300 mg of paracetamol.

Example 2

a) A crushed granulate is produced, analogously to Example 1 a), from 12,500 kg of oxyphenbutazone, 3,150 kg of lactose, 2,500 kg of dried maize starch, 0.500 kg of highly dispersed silicic acid, and 0.600 kg of polyvinylpyrrolidone; and from this granulate are then prepared, after addition of 0.600 kg of talcum and 0.150 kg of magnesium stearate, 100,000 tablet cores each weighing 200 mg.

b) A crushed granulate is first produced for the outer coating, analogously to Example 1 b), from 25,000 kg of paracetamol (particle-

size not exceeding 10 μm), 15,600 kg of mannitol, 2,000 kg of dried maize starch, and 0.600 kg of polyvinylpyrrolidone; and this granulate is then homogeneously mixed with 0.600 kg of talcum, 0.100 kg of magnesium stearate, and 0.100 kg of highly dispersed silicic acid, and the mixture compressed around the tablet cores obtained according to a).

In this manner are obtained 100,000 tablets each weighing 640 mg, and each containing 125 mg of oxyphenbutazone and 250 mg of paracetamol.

Example 3

250,000 g of oxyphenbutazone and 500,000 g of paracetamol are well mixed together, and homogeneously suspended in 1,750.00 g of cocoa butter, or in the same amount of saturated fatty acid glycerides having a melting point in the range of 33—37°C. From the obtained mass are poured 1000 suppositories each weighing 2.50 g, and each containing 250 mg of oxyphenbutazone and 500 mg of paracetamol.

In an analogous manner are produced, using 100.00 g of oxyphenbutazone, 200.00 g of paracetamol, and 800.00 g of cocoa butter, or saturated fatty acid glycerides having a melting point in the range of 33—37°C, 1000 suppositories each weighing 1.10 g and each containing 100 mg of oxyphenbutazone and 200 mg of paracetamol.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising oxyphenbutazone and paracetamol in combination with a pharmaceutically acceptable diluent or carrier therefor, there being present in said composition from 1 to 5 parts by weight of paracetamol per part by weight of oxyphenbutazone.

2. A pharmaceutical composition as claimed in claim 1 wherein from 2 to 4 parts by weight of paracetamol are present per part by weight of oxyphenbutazone.

3. A pharmaceutical composition as claimed in claim 1 or 2 compounded in unit dosage form for rectal or oral administration.

4. A pharmaceutical composition as claimed in claim 3 compounded in the form of a tablet, dragée or capsule for oral administration each such tablet, dragée or capsule containing from 25 to 150 mg of oxyphenbutazone and from 50 to 500 mg of paracetamol.

5. A pharmaceutical composition as claimed in claim 3 compounded in the form of a tablet, dragée or capsule for oral administration, each such tablet, dragée or capsule containing from 50 to 125 mg of oxyphenbutazone and from 100—250 mg of paracetamol.

6. pharmaceutical composition as claimed in claim 3 compounded in suppository or capsule form for rectal administration, each such suppository or capsule containing from 50 to 250 mg of oxyphenbutazone and from 100 to 500 mg of paracetamol.

7. A pharmaceutical composition as claimed in claim 3 compounded in suppository or capsule form for rectal administration, each such suppository or capsule containing from 100 to 250 mg of oxyphenbutazone and from 200 to 500 mg of paracetamol.

8. A pharmaceutical composition as claimed in claim 1 substantially as hereinbefore described with reference to any one of the Examples 1 to 3.

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2. A pharmaceutical composition as claimed in claim 1 wherein from 2 to 4 parts by weight of paracetamol are present per part by weight of oxyphenbutazone.

3. A pharmaceutical composition as claimed in claim 1 or 2 compounded in unit dosage form for rectal or oral administration.

4. A pharmaceutical composition as claimed in claim 3 compounded in the form of a tablet, dragée or capsule for oral administration each such tablet, dragée or capsule containing from 25 to 150 mg of oxyphenbutazone and from 50 to 500 mg of paracetamol.

5. A pharmaceutical composition as claimed in claim 3 compounded in the form of a tablet, dragée or capsule for oral administration, each such tablet, dragée or capsule containing from 50 to 125 mg of oxyphenbutazone and from 100—250 mg of paracetamol.

6. pharmaceutical composition as claimed in claim 3 compounded in suppository or capsule form for rectal administration, each such suppository or capsule containing from 50 to 250 mg of oxyphenbutazone and from 100 to 500 mg of paracetamol.

7. A pharmaceutical composition as claimed in claim 3 compounded in suppository or capsule form for rectal administration, each such suppository or capsule containing from 100 to 250 mg of oxyphenbutazone and from 200 to 500 mg of paracetamol.

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