

PATENT SPECIFICATION

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(54) SULPHONAMIDE SALT

- (71) We, MERCK M Co., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, or 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 pharmaceutical preparations, particularly tablets, containing probenecid, viz. *p*-(dipropylsulphamoyl) benzoic acid.

- 15 Probenecid-containing tablets of the past have been objectionable because of their slow disintegration time. As probenecid is one of the principal agents used to lessen the extreme pain of gout, it is important
 20 that the tablet disintegrate quickly after oral ingestion so that the probenecid is rapidly released and so that it can be absorbed systemically. Probenecid is also often given with penicillin, as the probenecid serves to prevent urinary excretion of the penicillin. In this use, the probenecid must be released quickly from the tablet so that its inhibitory activity against penicillin excretion will be available promptly.
 30 Past efforts to make a quickly disintegrable tablet containing probenecid have been unsuccessful because the tablets have been so fragile that they would not withstand transit shocks. Efforts to make a more
 35 rugged tablet have had the objection that their disintegration has been much too slow or has not occurred at all.

- The reason for the past inability to make quickly disintegrable tablets containing probenecid resided in the unusual physical nature of this drug. It is a rather sticky poorly compressible solid. To overcome these objectionable characteristics and to facilitate the tablet compression operation,
 45 large amounts of powdered excipients have

[Price 25p]

been added. The resulting compositions, while more dry and free-flowing, produced very fragile tablets. A sufficiently high compression to overcome this fragility has often resulted in a tablet of such firmness that it has disintegrated very slowly on ingestion. Indeed, this has even been reflected in the long disintegration time (60 minutes) allowable in the USP standard for probenecid tablets.

The present invention provides, as a new compound, the magnesium salt of probenecid in a tetrahydrate form, and a process for making it that comprises mixing together in a high intensity mixer probenecid, a magnesium inorganic acid salt, and water at 70°-90° at the rate of 400-600 ml per minute, maintaining the reaction mixture below 45°C and continuing the reaction until at least a 95% conversion of the starting magnesium salt to magnesium probenecid tetrahydrate has occurred. Magnesium probenecid is not sticky and therefore does not require an exceptionally large amount or any unusual powdered excipients for granulation and tablet compression. It has been found that a tablet made from probenecid of which at least 71% is in the form of magnesium probenecid tetrahydrate, although equally hard, will disintegrate in one-fourth to one-third of the time required for the hard non-fragile granulated tablets ordinarily made from the sticky probenecid. In addition to being in a dry readily compressible form, magnesium probenecid tetrahydrate also is water-soluble, while probenecid (acid) is quite insoluble.

Magnesium probenecid tetrahydrate is of especial value over the potassium salt because potassium ions are known to cause gastric distress. As relatively large amounts of probenecid (as its free acid) must be consumed daily, averaging about two grams, an excessive amount of potassium would be ingested in the case of potassium probenecid.

In like manner, sodium probenecid is objectionable because sodium is contraindicated in cardiac and hypertensive patients. Another advantage of the magnesium probenecid is that it tetrahydrate will withstand heating at a temperature up to 50°C without losing its water of hydration.

In order to provide a readily disintegrable magnesium probenecid tetrahydrate, it is important that the reaction be conducted under such controlled conditions so that the tetrahydrate form of the probenecid salt is formed and retained. To accomplish this the following conditions must be met:

- (a) a high intensity mixer must be used,
- (b) the probenecid and magnesium compound are added dry to the mixer, (c) warm water (70°-90°C) is added at the rate of 400-600 ml. and preferably 500 ml. per minute, (d) the reaction mixture is controlled so that the temperature does not exceed 45°C, e.g. by circulating cooling water around the reaction chamber, and (e) the operation is continued until a minimum conversion of 95% of the magnesium carbonate to the desired probenecid salt has taken place. Instead of the carbonate other inorganic acid salts such as magnesium phosphate may be used.

In this reaction, not all of the probenecid will be converted to the magnesium salt. Consequently, the product of the reaction mixture which is used in making the tablet should contain at least 71% of the probenecid in the form of magnesium probenecid tetrahydrate. That is, some unconverted probenecid may remain but unless at least 71% of the assayable probenecid present in the tablet is present as the magnesium probenecid tetrahydrate, the quick disintegration time which is a feature of tablets prepared from the compound of this invention will not be realized.

The magnesium probenecid tetrahydrate is used in making a granulation of a conventional nature. In the drying steps of the granulation procedure, however, care should be taken to keep a temperature below 50°C to prevent loss of the tetrahydrate form. Customary granulation additives may be used such as starch, gelatin and acacia a suitable one being a mixture of 2.100 kg. starch and 0.120 kg. gelatin. The granulation should be accomplished in a relatively short time such as 2 to 4 minutes.

The invention lends itself to the incorporation of other therapeutic agents. For example, penicillin can be added into the dried reaction mix prior to granulation so that the resulting tablet would contain about 250 mg. of probenecid (as the free acid) and 250,000 units of potassium penicillin. Or, colchicine may be added so that each tablet contains 0.5 mg. of colchicine and

500 mg. of probenecid (as the free acid).

Representative examples are the following:

EXAMPLE 1

30 Kg. Probenecid powder USP is dry-blended with 3.75 Kg. magnesium carbonate N.F. in a Littleford-Lodige or other high intensity mixer, 18 Kg. of water (80°-90°C) is added at the rate of 500 ml./minute. The reaction mixture is controlled at 40-50°C by circulation of water in the jacket of the mixture. The reaction is continued for one hour and assayed to ensure minimum 95-100% conversion of the magnesium carbonate to magnesium probenecid. The mixture is oven dried at a temperature not above 50°C and the dried mixture granulated with starch-gelatin paste (14.0 kg.) containing 2.100 Kg. starch and 0.120 Kg. gelatin. The granulation is performed in 2 to 4 minutes in a planetary mixer. The granulation is oven dried at a temperature not above 50°C blended with 10% corn starch and 1.0% calcium stearate and compressed at a maximum of 7400 lbs. pressure into tablets.

This preparation will prepare approximately 60,000 tablets, each containing the equivalent of 500 mg. of probenecid as the free acid. An adult having gout would take one or two of these tablets, three to four times daily. After ingestion, the magnesium probenecid tetrahydrate is hydrolysed rather quickly so that the free probenecid is released.

The tablets will be found to be strong enough to withstand shipping jolts and the tablets will be fully disintegrated in 10 to 30 minutes.

EXAMPLE 2

By substituting in Example 1, for the magnesium carbonate, an equivalent weight of magnesium phosphate, the desired magnesium probenecid tetrahydrate is obtained.

WHAT WE CLAIM IS:—

1. Magnesium probenecid tetrahydrate.
2. A pharmaceutical composition containing magnesium probenecid tetrahydrate as an active ingredient.
3. A pharmaceutical tablet containing magnesium probenecid tetrahydrate as an active ingredient.
4. A pharmaceutical tablet containing probenecid, at least 71% of which is in the form of magnesium probenecid tetrahydrate.
5. A tablet as claimed in claim 3 or 4 containing another therapeutic agent apart from the magnesium probenecid tetrahydrate and any residual probenecid.
6. The process that comprises mixing together in a high intensity mixer, probenecid, a magnesium inorganic acid salt, and water at 70°-90°C at the rate of 400-600 ml. per minute; maintaining the reaction mixture below 45°C and continuing the reaction until at least a 95% conversion of

In like manner, sodium probenecid is objectionable because sodium is contraindicated in cardiac and hypertensive patients. Another advantage of the magnesium probenecid is that it tetrahydrate will withstand heating at a temperature up to 50°C without losing its water of hydration.

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The invention lends itself to the incorporation of other therapeutic agents. For example, penicillin can be added into the dried reaction mix prior to granulation so that the resulting tablet would contain about 250 mg. of probenecid (as the free acid) and 250,000 units of potassium penicillin. Or, colchicine may be added so that each tablet contains 0.5 mg. of colchicine and

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This preparation will prepare approximately 60,000 tablets, each containing the equivalent of 500 mg. of probenecid as the free acid. An adult having gout would take one or two of these tablets, three to four times daily. After ingestion, the magnesium probenecid tetrahydrate is hydrolysed rather quickly so that the free probenecid is released.

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EXAMPLE 2

By substituting in Example 1, for the magnesium carbonate, an equivalent weight of magnesium phosphate, the desired magnesium probenecid tetrahydrate is obtained.

WHAT WE CLAIM IS:—

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2. A pharmaceutical composition containing magnesium probenecid tetrahydrate as an active ingredient.
3. A pharmaceutical tablet containing magnesium probenecid tetrahydrate as an active ingredient.
4. A pharmaceutical tablet containing probenecid, at least 71% of which is in the form of magnesium probenecid tetrahydrate.
5. A tablet as claimed in claim 3 or 4 containing another therapeutic agent apart from the magnesium probenecid tetrahydrate and any residual probenecid.
6. The process that comprises mixing together in a high intensity mixer, probenecid, a magnesium inorganic acid salt, and water at 70°-90°C at the rate of 400-600 ml per minute, maintaining the reaction mixture below 45°C and continuing the reaction until at least a 95% conversion of



the starting magnesium salt to magnesium probenecid tetrahydrate has occurred.

7. A process as claimed in claim 6 in which the magnesium inorganic acid salt is magnesium carbonate.

8. A process as claimed in claim 6, substantially as hereinbefore described in Example 1 or 2.

9. Magnesium probenecid tetrahydrate, when prepared by a process as claimed in claim 6, 7 or 8.

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