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PATENT SPECIFICATION (11) 1 445 983

(21) Application No. 51050/72 (22) Filed 6 Nov. 1972
(23) Complete Specification filed 5 Nov. 1973
(44) Complete Specification published 11 Aug. 1976
(51) INT CL² A61K 31/505
(52) Index at acceptance
A5B 384 38Y 502 50Y 552 575 576 57Y

1 445 983



(72) The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of The Patents Act 1949 are DAVID HARDEN, ALLAN JOHN TORODE, of 25 Sandhurst Road, Sidcup, Kent and 121 Gladwyns, Basildon, Essex, both British subjects. HENRY JOHN KESSLER of 8 Rose Street, White Plains, New York 10605 U.S.A. a citizen of the United States of America.

(54) PHARMACEUTICAL FORMULATIONS

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W. 12BP a company incorporated in England do hereby declare the invention, which was communicated from Burroughs Wellcome Co. of 3030 Cornwallis Road, Research Triangle Park, Noth Carolina 27709, U.S.A., a company incorporated in the State of North Carolina, United States of America, 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 formulations containing xanthine oxidase inhibitors for oral administration, and in particular to allopurinol tablets for use in the treatment of gout and other hyperuricaemic conditions.

Allopurinol, 4-hydroxypyrazolo(3,4-d)pyrimidine, is a potent inhibitor of the enzyme xanthine oxidase *in vivo*. It interferes with a metabolic pathway of the patient and prevents the formation of uric acid from hypoxanthine and xanthine by inhibiting the action of the enzyme xanthine oxidase. It is itself metabolised *in vivo* into the 4,6-dihydroxy analogue (oxipurinol), which inhibits the same system. In addition allopurinol can act as a substrate for the above enzyme thereby contributing to its overall effectiveness as an inhibitor for this system. Thus, when it has been administered to patients suffering from gout and other hyperuricaemic conditions, considerable success has been achieved.

Although daily dosages up to or even exceeding 1g have occasionally been recommended for administration to adult patients in special circumstances, the usual dosage is 100 mg allopurinol given two to four times per day. Such amounts of the medicament are normally administered in the form of a tablet, containing conventional excipients such as filling, granulating, lubricating and disintegrating agents, in addition to the 100 mg allopurinol representing about 30% of the weight of the formulation. Tablets provided in this manner are now well established in medical practice and have been taken by hundreds of thousands of patients several times a day, sometimes for a number of years.

In practice, divided daily doses were strongly recommended in the past because of the short half-life of less than 2 hours of allopurinol and a postulated risk of gastric intolerance. However, it has since been shown that oxipurinol has a longer half-life than allopurinol, *viz* between 18 and 40 hours, and, moreover, it has now been clinically established that a single dosage of 300 mg allopurinol taken at any time during the day can be as effective as 100 mg allopurinol taken thrice daily at spaced intervals during the day. Thus, the same uric acid levels are attainable in patients and both the urinary excretion of oxipurinol and oxypurines and the serum level of oxipurinol are substantially unchanged using either schedule. Furthermore, the LD_{50} value for a single dosage of 300 mg allopurinol in mice is not significantly different from the value for an equivalent plurality of dosages taken during the day.

There also appears to be no detrimental clinical effect resulting from the presence initially of the higher amount of drug in the body despite the fact that allopurinol and its metabolites act in a complex manner, and hence the former divided dosage regimen, which has hitherto always been recommended for reliable and smooth action, can advantageously be replaced by a single dosage schedule.

Since the clinical requirements for once-

a-day therapy can be satisfied, the replacement of several tablets with a single dosage established as the recommended treatment schedule would be advantageous for the majority of patients. Such a regimen would contribute substantially to the convenience of the patient who would need to take a tablet merely once during the day, for example after breakfast. This would enhance the probability of his taking the required amount of drug per day.

The single dosage scheme also lends itself applicable to the use of a tablet delivery device such as a "blister pack". For example, a month's supply of tablets could be arranged within a labelled card, the labels indicating the day on which the adjacent tablet is to be taken. The patient's task of routinely remembering to take his daily tablet would then be greatly simplified.

The provision of an increased dosage tablet to meet the newly created demands represented many problems. For example, considerable attention had to be given to the size of the tablet so that patient reluctance, arising from the administration of the tablet, which could occur if the tablet was too large, is obviated. Therefore, on increasing the proportion of allopurinol, the size of the tablet must be kept sufficiently small without endangering the efficacy of the tablet as a whole.

Since allopurinol is a drug which is usually administered to patients with chronic disease over long periods of time, the above considerations assume considerable importance.

Moreover, difficulties would be encountered in the preparation of an increased dosage tablet which has a sufficiently rapid disintegration time coupled with a satisfactory degree of hardness.

It has now been found that a tablet formulation having all the necessary characteristics of a high quality tablet can be achieved with a higher proportion of allopurinol present than has hitherto been obtained. These formulations, containing, for example, about 60% (w/w) of allopurinol, lend themselves particularly for use in the aforementioned increased dosage tablet.

Such a high content of active ingredient in a tablet has now been made possible by a reduction in the content of other excipients, such as the inert filler usually present in relatively high proportions in conventional tablets, and also using allopurinol having a particle size, as hereinafter defined, less than 40 μm.

Accordingly, the present invention provides a tablet formulation which comprises from 55 to 79% (w/w) of allopurinol having a particle size, as hereinafter defined, less then 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

In particular, the formulation comprises from 55 to 65% (w/w) of allopurinol and from 15 to 30% (w/w), preferably from 25 to 30% (w/w) of inert filler. Moreover, formulations comprising 12 or 13% (w/w) of disintegrating agent and from 1 to 5% (w/w) of granulating agent are further preferred.

A formulation containing from 250 to 350 mg, for example 300 mg, constitutes a most preferred aspect of this invention.

Inert fillers which may be employed in the present invention include dicalcium phosphate, microcrystalline celluloses, such as Avicel (Trade Mark), mannitol or, preferably lactose.

Disintegrating agents which may be employed in the present invention include alginic acid, sodium starch glycolate, for example Primojel, suitable guar based vegetable gums, such a Supercol (Trade Mark) U or Supercol Gf, calcium carboxymethyl celluloses, for example ECG 505, or preferably starch in view of its ready availability and cost advantage.

Granulating agents which may be employed in the present invention include starch in the form of mucilage, starch derivatives, such as starch "Snow Flake" (marketed by Corn Products (Sales) Ltd.), cellulose derivatives, such as methylcellulose, gelatin and preferably polyvinylpyrrolidine.

The required low disintegration time and satisfactory hardness of the formulation, coupled with the necessity for high reproducibility of the physical characteristics associated with a conventional allopurinol tablet, can be achieved if the above conditions are combined with the requirement that the particle size, as hereinafter defined, of allopurinol is kept below 40 μm, for instance between 28 to 38 μm. The particular particle size, will depend on the envisaged content of allopurinol in a tablet. If, for example, 50% (w/w) of allopurinol is required, then the particle size could be, for instance, between 28 and 38 μm. On the other hand, if a 75% (w/w) content of active ingredient is required, it is advisable to use allopurinol having an even lower particle size, for example 15 to 28 μm.

The particle size of allopurinol may readily be reduced by crystallisation techniques or by grinding the particles with any apparatus or by any other method in the art suitable for such a purpose. In particular, the hammer mill, which can be

used with either rigid or the swing-hammer type and is conveniently combined with a fan and a cyclone for collecting the material, is preferred.

Particles of allopurinol form elongated, tetragonal prisms but after grinding these prisms give rise to rounded rods and irregular spheres and, as used hereinbefore, the particle size is defined in terms of the "weight median diameter" hereinafter referred to as W.M.D., of a hypothetical sphere of identical volume, i.e. that "diameter", wherein 50% of the equivalent spheres have a larger diameter and 50% a smaller diameter than that figure. The W.M.D. may be determined using a Coulter counter in which the allopurinol powder, previously dispersed in an electrolyte comprising an aqueous solution of, for example, sodium chloride saturated with allopurinol, is passed through a small orifice in a tube on either side of which is immersed an electrode. The changes in resistance as particles pass through the orifice generate voltage pulses whose amplitudes are proportional to the volumes of the particles. The pulses are amplified, and the numbers counted at different threshold levels. From this data the size distribution of the suspended particles and hence the W.M.D. may be determined.

It may also be desirable to include a small proportion of a suitable lubricant, such as magnesium stearate, in the tablet formulation so that the tablet is thereby prevented from adhering to the punches and dies of the automatic tabletting equipment. Also, dyes and preservatives may be added, if required.

It should be appreciated that since a rapid disintegration time is usually associated with a low hardness for the type of drug having the physical characteristics of allopurinol, the various requirements have to be carefully balanced and it would be very surprising to provide a tablet of reasonable size with a relatively high allopurinol content e.g. 300 mg, without applying the conditions laid down by the present invention.

Apart from the proportions of components specified above and the stated quality requirements, the tabletting procedure is carried out according to the methods of normal practice in pharmaceutical manufacture. Thus, the ingredients are mixed in a dried state, usually at a slow speed, for example around 15 rev/min, in a planetary mixer, followed by wet mixing for up to about 30 minutes with a granulating solution, together with additional solvent, if necessary, for maintaining the consistency of the mass. The material is then milled and is tray-dried at about 50°C for several hours or alternatively dried in a fluidised bed at around 60°C for about 30 minutes. The dry material is sifted and a lubricant is added to the granules provided in this manner. Compression of the granules in standard machinery to the specified hardness then gives tablets of the required size and shape.

Accordingly in another aspect of the invention, there is provided a method of preparing a tablet formulation which comprises admixing from 55 to 79% (w/w) of allopurinol having a particle size less than 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

As used herein, the term (w/w) is used to denote the ratio of the weight of specified excipient to the total weight of the tablet formulation.

The disintegration time may be determined by the method described in the British Pharmacopoeia 1968 which involves the rapid movement of the tablet in water under standardised conditions, until there are no fragments remaining above a supporting wire gauge (*vide* pages 1366 to 1367).

The British Pharmacopoeia 1968 also states that the disintegration time for any tablet must not exceed 15 minutes, but desirably this time should be less than 10 minutes, especially below 5 minutes, for safety reasons in view of inevitable variations from tablet to tablet. In the United States Pharmacopoeia XVIII (1970) a specific maximum disintegration time for allopurinol is given as 45 minutes. In addition to this essential requirement it is generally recommended that the moisture content of the granule from which the tablet is produced should be below 2% since additional moisture is inevitably absorbed on subsequent exposure to air before or after compression. Substantially higher moisture contents, e.g. 3%, involve the risk of mould growth.

The "hardness" of a tablet is the amount of force required to shatter it or is more correctly the crushing strength, and although this may be measured accurately according to various standards, the Monsanto (Trade Mark) method is convenient and suitable for testing the tablet produced in accordance with the present invention. Basically the method involves the use of a Monsanto (Trade Mark) Tablet Hardness Tester, which is a spring-loaded device capable of exerting radial pressure on an edge of the tablet, the shattering force being read from a scale on the sleeve of the device.

The friability of a tablet is a measure of the loss of weight suffered by a tablet from

abrasion or shock and may be tested by a "Roche" Friabilitor in which a weighed sample of tablets is subjected in the apparatus to abrasion during a tumbling action, comparable to tablets rubbing one another or being shaken against the walls of their container in general use, and to a shock resulting from a free-fall of six inches, such as might be encountered during various steps in packaging, handling and transport.

The dissolution time of a tablet may, for instance, be determined according to the U.S.P. XVIII by using an apparatus comprising a cylindrical basket of 1680 μm stainless steel mesh, a covered 100 ml glass vessel, a constant-temperature water bath, and a variable-speed motor. The dissolution medium, which may be for example 0.6% hydrochloric acid, pH 1.2, for allopurinol, is poured into the vessel which has been previously immersed in the constant-temperature bath and the medium is allowed to come to a temperature of 35°C. A tablet is placed in the basket and the apparatus assembled such that the basket is fully immersed in the medium. The basket is rotated at, for example, 120 rev/min. and samples are withdrawn at intervals with a syringe and assayed, for instance, by U.V. absorbance.

Further advantages of the present invention will now become apparent from the following description of embodiments of the invention, which embodiments do not limit this invention in any way.

Example I

Allopurinol (3.0 kg) having a particle size of 33 μm, dried maize starch (700 g) and lactose (1.5 kg) were hand sifted through a 150 μm sieve, a 125 μm sieve and a further 125 μm sieve respectively transferred into a planetary mixer and mixed for 10 minutes at 14 r.p.m.

A granulating solution containing polyvinylpyrrolidine (140 g), alcohol (420 g) and purified water (140 g) was prepared and to this solution more solvent (650 ml) containing 2 volume parts of alcohol and 1 volume part of purified water was added as a rinse and to maintain granulating wetness. The resulting solution was then wet-mixed with the powders for 15 minutes using slow-speed stirring as above.

Granulation was carried out in a comminuting mill, using a 1.30 cm screen and the material was subsequently dried in a fluidised bed at 60°C for 30 minutes to a moisture content of 0.66% prior to sifting through a 1000 μm screen.

Magnesium stearate (24 g) was added to the granules and the resulting mixture compressed on a Manesty (Trade Mark) BB3 rotary compression machine to provide tablets having a hardness value of 12 kg (Monsanto), a disintegration time of 2 min. 50 sec. and a friability value of 0.075%. The time for 50% of the tablet to dissolve in 0.6% HCl (pH 1.2), hereinafter referred to as T_{50}, and the time for 80% of the tablet to dissolve in 0.6% HCl (pH 1.2), hereinafter referred to as T_{80}, were 3 min. and 5 min. 12 sec. respectively.

Each of the tablets had a thickness of 5 mm, a weight of 537 mg and contained 300 mg. of allopurinol.

The above procedure was repeated for a tablet formulation which also included finely sifted F.D and C yellow NO. 6, Lake Dispersed, the dye being added before passing the resultant mixture through the 150 μm sieve.

The resulting tablets had physical characteristics substantially identical to those obtained above.

Example II

The process of Example I was repeated, the wet mixing time being increased however from 15 to 30 minutes. The granules having a moisture content of 0.56% were compressed to provide tablets having a hardness value of 10 kg (Monsanto), a disintegration time of 3 min. 30 sec. and a friability value of 0.075%. The T_{50} and T_{80} values were respectively 2 min. and 4 min.

Each tablet weighed 533 mg and contained 300 mg of allopurinol.

Example III

The process was carried out as described in Example I except that the wet-mixing time was only 5 minutes and an increased volume of additional solvent (1000 ml) containing 2 volume parts of alcohol and 1 volume part of purified water was added. The granules having a moisture content of 0.65% were compressed to provide tablets having a hardness value of 10 kg (Monsanto), a disintegration time of 3 min. 20 sec. and a friability value of 0.08%. The T_{50} and T_{80} values were respectively 2 min. and 4 min.

Each tablet weighed 537 mg and contained 300 mg of allopurinol.

Example IV

Allopurinol (3 kg) having a particle size of 39 μm, dried maize starch, (570 g) and lactose (1.015 kg) were hand-sifted as described in Example I and mixed in a planetary mixer for 10 minutes at 14 rev/min. A granulating solution containing polyvinylpyrrolidine (140 g), alcohol (420 g) and purified water (140 g) was prepared, and the additional solvent, comprising 2 volume parts of alcohol and 1 of purified water, was added to this to impart sufficient granulating wetness. The resulting solution

was then wet-mixed with the powders for 5 minutes using a slow speed initially and then a medium speed setting.

Granulation was carried out in a comminuting mill fitted with a 0.6 cm screen and running at a medium speed. The granules were subsequently dried in a fluidised bed at 60°C for 30 minutes to a moisture content of 0.89% prior to sifting through a 1000 μm screen. Magnesium stearate (24 g), sifted 250 μm fine, was mixed in with a blender for 10 minutes and the resulting granules compressed on a Manesty D3 Rotary Machine to provide tablets having a hardness value of 10 or 12 kg (Monsanto), a disintegration time of 3 min. 52 sec. or 4 min. 45 sec. respectively and friability values of less than 0.2%.

Each tablet weighed 475 mg and contained 300 mg of allopurinol.

Example V

The procedure of Example IV was followed except that only 9.59 g of magnesium stearate was added in the lubricating stage. The granules having a moisture content of 0.9% were compressed to provide tablets containing 300 mg of allopurinol and having a hardness value of 10 or 12 kg (Monsanto), a disintegration time of 2 min. 40 sec. or 2 min. 55 sec. respectively and friability values of less than 0.2%.

Owing to the lower proportion of magnesium stearate present, there was a simultaneous reduction, however, in the efficiency of the lubricant.

Example VI

Allopurinol having a particle size of 45 μm was passed through an Apex (Trade Mark) comminuting mill fitted with a B.1762 screen. The mill was run at medium speed with the cutter blades forward to provide allopurinol having a particle size of 28μm.

A similar experiment to that in Example IV was then conducted using the ground allopurinol. Also, the granules were tray-dried in an oven at 50°C for 4 hours and the quantity of magnesium stearate adjusted to 10 g.

The granules were compressed to provide tablets having a hardness value of 9.5 kg (Monsanto), disintegration time of 2 min. 30 sec. and a friability value of less than 0.2%.

Each tablet weighed 474 mg and contained 300 mg allopurinol.

Example VII

Allopurinol (3 kg) having a particle size of 39 μm, dried maize starch, (570 g) and lactose (1.5 kg) were granulated as described in Example IV and dried in a fluidised bed at 60°C for 30 minutes. Magnesium stearate (26 g) was mixed in, and the resulting granules having a moisture content of 0.61% compressed to provide tablets having a hardness value of 10 or 12 kg (Monsanto), a disintegration time of 2 min. 50 sec. or 4 min. 50 sec. respectively and a friability value of less than 0.2%.

Each tablet weighed 510 mg and contained 300 mg allopurinol.

Example VIII

The quantities of starting materials quoted in Example IV were mixed together in the dry state for 15 minutes at a slow speed and then wet-mixed with a solution containing polyvinylpyrrolidine (140) alcohol (1207 g) and pure water (402 g) for 5 minutes using initially a slow speed and then a medium speed.

Granulation was carried out in a comminuting mill fitted with a 0.95 cm screen and running at medium speed and the granules were subsequently tray-dried at 50°C for 4 hours. The dried granules were sifted through a 1000 μm screen and magnesium stearate (10 g), 250 μm fine, subsequently added. The granules were compressed on an R.B.2 Rotary Machine to provide tablets having a hardness value of 10 to 12 kg (Monsanto), a disintegration time of 13 min. 5 sec. and a friability value of 0.23%.

Each of the tablets had a thickness from 4.8 to 4.9 mm, a weight of 475 mg and contained 300 mg of allopurinol.

Example IX

Allopurinol (1.0 kg) having a particle size of 39 μm, mannitol (235.4 g), Primojel (110 g) and pre-gelled starch (117.7 g) were mixed in the dry state for 10 minutes. Purified water (200 ml) was added to and subsequently mixed with the powders for 10 minutes. The resultant wet mass was passed through a 1000 μm sieve to produce granules which were then dried in a fluidised bed at 60°C for 30 minutes to a moisture content of 1.59% prior to sifting through a 1000 μm screen.

Magnesium stearate (7.4 g), previously sifted through a 250 μm sieve, was blended with the granules and the subsequent mixture compressed on a Manesty D3 rotary machine to provide tablets having a hardness value (Monsanto) of 9.0 kg, a disintegration time of 3 min. 30 sec. and a friability value of less than 0.1%.

Each of these tablets had a thickness of 4.17 mm, a weight of 379 mg and contained 270 mg of allopurinol.

Example X

The process of Example IX was repeated except that the mixture was compressed on a Manesty D3 rotary machine to provide

tablets having a hardness value (Monsanto) of 9.0 kg, a disintegration time of 2 min. 45 sec. and a friability value of less than 0.1%.

Each of these tablets had a thickness 4.17 mm, a weight of 379 mg and contained 270 mg of allopurinol.

Example XI

Allopurinol (1.0 kg) having a particle size of 15μm, dicalcium phosphate (139.4 g) and Alginate YZ (105.4 g) were mixed in the dry state for 10 minutes. A granulating solution containing gelatin (66.0 g), purified water (165 g) and alcohol (80.0 g) was prepared and the solution wet-mixed with the powders for 10 min. The wet mass was passed through a 1000 μm sieve and the resultant granules dried in a fluidised bed at 60°C for 30 min. to a moisture content of 1.37% prior to sifting through a 1000 μm screen.

Magnesium stearate (6.7 g), previously sifted through a 125 μm sieve was added to the dried granules and the subsequent mixture compressed on a Manesty D3 rotary machine to provide tablets having a hardness value (Monsanto) of 12.0 kg, a disintegration time of 6.0 min. and a friability value of less than 0.1%.

Each tablet had a thickness of 4.38 mm, a weight of 395.2 mg and contained 300 mg of allopurinol.

Example XII

The process of Example XI was repeated except that the mixture was compressed on a Manesty D3 rotary machine to provide tablets having a hardness value (Monsanto) of 10.0 kg, a disintegration time of 5 min. 30 sec. and a friability value of less than 0.1%.

Each of these tablets had a thickness of 4.6 mm, a weight of 421.5 mg and contained 320 mg of allopurinol.

WHAT WE CLAIM IS:—

1. A tablet formulation which comprises from 55 to 79% (w/w) of allopurinol having a particle size, as hereinbefore defined, less than 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

2. A tablet formulation according to claim 1, which comprises from 55 to 65% (w/w) of allopurinol.

3. A tablet formulation according to either of claims 1 and 2, which comprises from 15 to 30% (w/w) of an inert filler.

4. A tablet formulation according to claim 3, which comprises from 25 to 30% (w/w) of an inert filler.

5. A tablet formulation according to any one of the preceding claims, which comprises 12 or 13% (w/w) of a disintegrating agent.

6. A tablet formulation according to any one of the preceding claims, which comprises from 1 to 5% (w/w) of a granulating agent.

7. A tablet formulation according to any one of the preceding claims, which comprises from 250 to 350 mg of allopurinol.

8. A tablet formulation according to claim 7, which comprises about 300 mg of allopurinol.

9. A tablet formulation according to any one of the preceding claims, which comprises allopurinol having a particle size from 15 to 38 μm.

10. A tablet formulation according to claim 9, which comprises allopurinol having a particle size less than or equal to 28 μm.

11. A tablet formulation according to claim 9, which comprises allopurinol having a particle size greater than 28 μm.

12. A tablet formulation according to any one of the preceding claims, wherein the inert filler is lactose.

13. A tablet formulation according to any one of the preceding claims, wherein the disintegrating agent is starch.

14. A tablet formulation according to any one of the preceding claims, wherein the granulating agent is polyvinylpyrrolidine.

15. A tablet formulation substantially as herein described with reference to any one of Examples I to XII.

16. A method of preparing a tablet formulation according to any one of the preceding claims which comprises admixing from 55 to 79% (w/w) of allopurinol having a particle size, as hereinbefore defined, less than 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

tablets having a hardness value (Monsanto) of 9.0 kg, a disintegration time of 2 min. 45 sec. and a friability value of less than 0.1%.

Each of these tablets had a thickness 4.17 mm, a weight of 379 mg and contained 270 mg of allopurinol.

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Allopurinol (1.0 kg) having a particle size of 15μm, dicalcium phosphate (139.4 g) and Alginate YZ (105.4 g) were mixed in the dry state for 10 minutes. A granulating solution containing gelatin (66.0 g), purified water (165 g) and alcohol (80.0 g) was prepared and the solution wet-mixed with the powders for 10 min. The wet mass was passed through a 1000 μm sieve and the resultant granules dried in a fluidised bed at 60°C for 30 min. to a moisture content of 1.37% prior to sifting through a 1000 μm screen.

Magnesium stearate (6.7 g), previously sifted through a 125 μm sieve was added to the dried granules and the subsequent mixture compressed on a Manesty D3 rotary machine to provide tablets having a hardness value (Monsanto) of 12.0 kg, a disintegration time of 6.0 min. and a friability value of less than 0.1%.

Each tablet had a thickness of 4.38 mm, a weight of 395.2 mg and contained 300 mg of allopurinol.

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Each of these tablets had a thickness of 4.6 mm, a weight of 421.5 mg and contained 320 mg of allopurinol.

WHAT WE CLAIM IS:—

1. A tablet formulation which comprises from 55 to 79% (w/w) of allopurinol having a particle size, as hereinbefore defined, less than 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

2. A tablet formulation according to claim 1, which comprises from 55 to 65% (w/w) of allopurinol.

3. A tablet formulation according to either of claims 1 and 2, which comprises from 15 to 30% (w/w) of an inert filler.

4. A tablet formulation according to claim 3, which comprises from 25 to 30% (w/w) of an inert filler.

5. A tablet formulation according to any one of the preceding claims, which comprises 12 or 13% (w/w) of a disintegrating agent.

6. A tablet formulation according to any one of the preceding claims, which comprises from 1 to 5% (w/w) of a granulating agent.

7. A tablet formulation according to any one of the preceding claims, which comprises from 250 to 350 mg of allopurinol.

8. A tablet formulation according to claim 7, which comprises about 300 mg of allopurinol.

9. A tablet formulation according to any one of the preceding claims, which comprises allopurinol having a particle size from 15 to 38 μm.

10. A tablet formulation according to claim 9, which comprises allopurinol having a particle size less than or equal to 28 μm.

11. A tablet formulation according to claim 9, which comprises allopurinol having a particle size greater than 28 μm.

12. A tablet formulation according to any one of the preceding claims, wherein the inert filler is lactose.

13. A tablet formulation according to any one of the preceding claims, wherein the disintegrating agent is starch.

14. A tablet formulation according to any one of the preceding claims, wherein the granulating agent is polyvinylpyrrolidine.

15. A tablet formulation substantially as herein described with reference to any one of Examples I to XII.

16. A method of preparing a tablet formulation according to any one of the preceding claims which comprises admixing from 55 to 79% (w/w) of allopurinol having a particle size, as hereinbefore defined, less than 40 μm, from 15 to 35% (w/w) of an inert filler, from 5 to 15% (w/w) of a disintegrating agent and from 1 to 10% (w/w) of a granulating agent.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.