PATENT SPECIFICATION (11) 1 460 302

1 460 302

(21) Application No. 24628/73 (22) Filed 23 May 1973
(23) Complete Specification filed 23 May 1974
(44) Complete Specification published 6 Jan. 1977
(51) INT. CL.[2] A61K 9/20 31/505
(52) Index at acceptance
A5B 381 384 38Y 39X 502 50Y 552 55Y 575 576 57Y 750 753 759 75Y

(72) Inventors DAVID HARDEN
ALLAN JOHN TORODE

(19)

(54) TABLET FORMULATION

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183-193 Euston Road, London, N.W. 1., a company incorporated in England 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 formulatons, 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 300mg 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.

Moreover, difficulties are frequently encountered in the preparation of a tablet with a high content of active ingredient but which retains a sufficiently rapid disintegration time coupled with a satisfactory degree of hardness.

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.

It has now been found that a tablet having excellent characteristics can be manufactured with a higher proportion of allopurinol present than has hitherto been obtained. These tablets, containing, for example, about 95% (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 been made possible by using allopurinol having a particle size, as hereinafter defined, from 2 to 40 μm and also by a reduction in the content of the inert filler component, usually present in relatively high portions in conventional tablets, to a minimum or, more preferably and even unexpectedly, by omitting this component completely.

When this technique is applied to the preparation of the increased dosage tablet, i.e. a tablet containing 300 mg of allopurinol, the resulting formulation not only bears great resemblances in size and physical characteristics to the conventional 100 mg tablets but it also possesses a pharmacological activity in mammals which is virtually identical with the same activity of an equivalent plurality of conventional tablets when administered over a given time, such as 24 hours.

Accordingly, the present invention provides a tablet formulation which comprises from 80 to 98% (w/w) of allopurinol having a particle size, as hereinafter defined, from 2 to 40μm, from 1 to 19% (w/w) of a disintegrating agent and from 1 to 19% (w/w) of a granulating agent.

In particular, the formulation comprises at least 85% (w/w), preferably at least 90% (w/w), for example 95% (w/w), of allopurinol. Moreover, formulations comprising less than 5% (w/w), for example about 2% (w/w), of a granulating agent and less than 5% (w/w), for example about 2% (w/w), of a disintegrating agent are further preferred.

A tablet formulation wherein each tablet contains either from 250 to 350 mg, for example 300 mg, or from 50 to 150 mg, for example 100 mg, of allopurinol constitutes a most preferred aspect of this invention.

Particles of allopurinol form elongated, tetragonal prisms but after grinding these prisms give rise to rounded rods and irregular spheres and, as used herein, the particle size is defined in terms of the 'weight median diameter' hereinafter referred to as W.M.D. Thus each particle is considered as a sphere having a volume identical with the actual particle and the W.M.D. is that 'diameter' wherein 50% of the equivalent spheres have a larger diameter than that figure 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.

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.

The actual particle size of allopurinol which should be used will depend on the envisaged content of allopurinol in the tablet. If, for example, 80% (w/w) content of allopurinol is required, then the average particle size could be, for instance, from

28 to 38μm. On the other hand, if a 95% (w/w) content of active ingredient is required, it is advisable to keep the particle size below 28μm, preferably below 15μm, for example about 10μm.

Disintegrating agents which may be employed in the present invention include alginic acid, a sodium starch glycolate, guar based vegetable gums, such as Supercol U (Trade Mark) or Supercol F (Trade Mark), calcium carboxymethyl cellulose such as ECG 505, and, most preferably, Primojel (Trade Mark).

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

From 0.09 to 0.4% (w/w) of a surface active agent suitable for promoting rapid disintegration, such as dioctyl sodium sulphosuccinate, may be included in the tablet formulation. However, it is further preferred to use 0.05 to 0.6% (w/w) of a surface active agent, such as dioctyl sodium sulphosuccinate, in combination with 0.1 to 1.0% (w/w) of finely divided silica, such as Aerosil (Trade Mark). This combination, particularly when used in a weight ratio from 3:1 to 1:5 (surface active agent: finely divided silica), has been found to be of even greater assistance in promoting fast disintegration and yet still conducive to a very satisfactory hardness in a tablet of the present invention.

It is desirable to include a small proportion, e.g. about 1% (w/w), 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 tableting equipment. Also, dyes, such as Certolake Sunset Yellow or Sunset Yellow C.F.S. and preservatives such as Nipagin M (a Registered Trade Mark) (methyl-p-hydroxybenzoate), may be added, if required.

Of course, with a relatively low content of allopurinol present, e.g. 80 to 90% (w/w), it will be necessary to either increase the proportions of the other components such as the disintegrating and granulating agents, or to have some inert filler present as well to make up the proportions to 100% (w/w).

Fillers that may be employed in the practice of the present invention include dicalcium phosphate, microcrystalline celluloses, such as Avicel (Trade Mark), mannitol, or preferably lactose. Although it is preferred that the inert filler rather than one of the other components is used to make up the proportions to 100%, it is even further preferred, and is indeed one of the advantages of this invention, to have a high content of allopurinol, e.g. 90 to 95% (w/w) present whereby the problem of addition or further addition of a component to make up the formulation to 100% is obviated.

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 has been very difficult, or even found virtually impossible, to provide a tablet of similar size to the conventional tablet yet with a higher allopurinol content, e.g. 300mg, without applying the conditions laid down by the present invention.

Apart from the proportion of components specified above and the stated quality requirements, the tabletting procedure may conveniently be 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 of aqueous alcohol and a granulating agent 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 the 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 and the product is then tested to check conformity with the standards of the British or United States Pharmacopoeia.

Accordingly, the present invention further provides a method of preparing a tablet, which comprises the compression on standard machinery of a formulation containing from 80 to 98% (w/w) of allopurinol having a particle size, as hereinbefore defined, from 2 to 40μm, from 1 to 19% (w/w) of a disintegrating agent and from 1 to 19% (w/w) of a granulating agent.

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

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 sup-

porting wire guage (*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 1% (w/w) since additional moisture is inevitably absorbed on subsequent exposure to air before or after compression. Substantially higher moisture contents, e.g. 3% (w/w), 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 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 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 1680μm stainless steel mesh, a covered 1000 ml glass vessel, a constant-temperature water bath, and a variable-speed motor. The dissolution medium, which may be for example 0.6% of 32% concentrated hydrochloric acid (v/v), 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 37°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 become apparent from the following description of the embodiments of the invention, which embodiments however do not limit the present invention in any way.

Example 1

Allopurinol was ground down to a particle size having a W.M.D. of 10μm using a Micropul mill connected to an air filter system of No. 2 Pallman mill.

Allopurinol (5.0 Kg.) and Primojel (100 g.) were mixed in a planetary mixer for 10 minutes at 14 rev/min. A granulating solution containing gelatin (100 g.), Sunset Yellow, Lake Dispersed (2.5 g.), dioctyl sodium sulphosuccinate (10.0 g.), purified water (520 g.) and alcohol (400 g.) was prepared. The solution was wet-mixed with the powders for 15 minutes using slow speed. 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 20 minutes to a moisture content of 0.4% (w/w) prior to sifting through a 1000 μm screen. Magnesium Sterate (50 g.) and Aerosil 200 (31.7 g.) were blended with the granules. The granules were compressed on a Manesty B.B.3 Rotary Machine to provide tablets containing 300 mg. allopurinol and having a hardness value of 12.0 Kg. (Monsanto), a disintegration time of 6 min. 54 sec. and a friability value of less than 0.5%. When compressed at 7.0 Kg hardness the disintegration time was reduced to 3 min. 14 sec. and the friability value increased to 3%. The time for 50% of the tablet to dissolve in 0.6% of 32% concentrated HCL (v/v) (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}, was 2.5 and 10 min. respectively. Each of the tablets weighed 317.65 mg. and contained 300 mg. of allopurinol.

Example 2

Allopurinol (5.0 Kg.) prepared as in Example 1, Primojel (105. g.) and Sunset Yellow Lake Dispersed (16.6 g.) were mixed in a planetary mixer for 10 minutes at 14 rev/min. A granulating solution containing gelatin (83.3 g.), purified water (416 g.) and alcohol (300 g.) was prepared. The solution was wet-mixed with the powders for 15 minutes using slow speed.

Granulation was carried out in a comminuting mill fitted with 0.6 cm. screen and running at a medium speed. The granules were subsequently dried in an oven on trays at 60°C for 12 hours to a moisture

content of 0.35% (w/w) prior to sifting through a 1000μm screen. Magnesium stearate (50 g.) sifted through 250μm screen, was blended with the granules. The granules were compressed on a Manesty B.B.3 Rotary Machine to provide tablets containing 300 mg. allopurinol and having a hardness value of 9.5 Kg. (Monsanto), a disintegration time of 5 min. 06 sec. and a friability value of less than 0.5%. The T_{50} and T_{80} values were respectively 3 and 10 min. Each of the tablets weighed 315.5 mg. and contained 300 mg. of allopurinol.

Example 3

Allopurinol (5.0 Kg.), prepared as in Example 1, Primojel (100 g.) and Sunset Yellow, Lake Dispersed (16.6 g.) were mixed in a planetary mixer for 10 minutes at 14 rev/min. A granulating solution containing gelatin (83.3 g.), purified water (416. g.), dioctyl sodium sulphosuccinate (10 g.) and alcohol (300 g.) was prepared. The solution was wet-mixed with the powders for 15 mins. using slow speed. Granulation was carried out in a comminuting mill fitted with 0.6 cm. screen and running at medium speed. The granules were subsequently dried in a fluidised bed at 60°C for 20 minutes to a moisture content of 0.4% (w/w) prior to sifting through a 1000 μm screen. Magnesium stearate (50 g.), sifted through a 250 μm screen, was blended with the granules. The granules were compressed on a Manesty B.B.3 Rotary Machine to provide tablets containing 300 mg. allopurinol and having a hardness value of 7 Kg. (Monsanto), a disintegration time of 3 min. 10 secs. and a friability value of less than 0.5%. Each of the tablets weighed 315.6 mg. and contained 300 mg. of allopurinol.

Example 4

Allopurinol (5.0 Kg.), prepared as in Example 1, Primojel (108 g.) were mixed in a planetary mixer for 10 minutes at 14 rev/min. A granulating solution containing gelatin (91.7 g.), Sunset Yellow F.C.F., B.S.S. (2.5 g.) purified water (458 g.) and alcohol (300 g.) was prepared. The solution was wet-mixed with the powders for 15 minutes using slow speed. The granules were subsequently dried in a fluidised bed at 60°C for 20 minutes to a moisture content of 0.25% (w/w) prior to sifting through a 1000 μm screen. Magnesium stearate (50 g.), sifted through a 250μm screen, was blended with the granules. The granules were compressed on a Manesty B.B.3 Rotary Machine to provide tablets containing 300 mg. allopurinol and having a hardness value of 10 Kg. (Monsanto), a disintegration time of 15 min. 40 sec. and a friability value of less than 0.5%. The T_{50} and T_{80} were respectively 8 and 28 min. Each of the tablets weighed 315.15 mg. and contained 300 mg. of allopurinol.

Example 5

Allopurinol (1.0 kg), prepared as in Example 1, and Primojel (50.0 g) were mixed for 10 minutes. A granulating solution containing gelatin (33.4 g), dioctyl sodium sulphosuccinate (2.0 g), purified water (83.0 g) and alcohol (40.0 g) was prepared. The solution was wet-mixed with the powders for 10 minutes.

After sifting 1000μm B.S.S. the granules were dried in a fluidised bed at 60°C for 20 minutes to a moisture content of 0.63% (w/w).

The dried granules were sifted through a 1000μm screen and Magnesium Stearate (10.0 g) and Aerosil (6.7 g) were blended with the granule.

The granules were compressed on a Manesty D.3 Rotary Machine to provide tablets containing 300 mg allopurinol and having a hardness value of 12.0 kg (Monsanto), a disintegration time of 5 mins. 57 secs. and a friability of 0.5%. The T_{50} and T_{80} Values were 5 mins. and 11 mins. respectively.

Example 6

Allopurinol (1.0 kg), having a W.M.D. of 38μm, Primojel (84.3 g) and Lactose (66.7 g) were mixed for 10 minutes.

The mixture was then granulated and compressed as in Example 5; the granules having been dried to a moisture content of 0.58% (w/w). The tablets had a hardness value of 10 kg (Monsanto), a disintegration time of 6 mins. 40 secs. and a friability of 0.32%. The T_{50} and T_{80} Values were 6 mins. and 10 mins. respectively.

Example 7

Allopurinol (1.0 kg), prepared as in Example 1, and maize starch (200 g) were mixed for 10 mins. A granulating solution containing polyvinylpyrrolidone K.30 (33.3 g), purified water (150 g) and alcohol (120 g) was prepared. The solution was wet-mixed with the powders for 10 minutes.

The resulting wet-mixture was then sifted as in Example 5, dried to a moisture content of 1.25% (w/w) and compressed as in Example 5.

The tablets had a hardness value of 10 kg (Monsanto), a disintegration time of 2 mins. 10 secs. and friability of 0.49%. The T_{50} and T_{80} Values were 2 mins. and 4 mins. respectively.

Example 8

Allopurinol (1.0 kg), prepared as in Example 1, pre-gelled starch (200 g) and Primojel (33.3 g) were mixed for 10 minutes. Purified water (550 g) was wet-mixed with the powders for 10 minutes.

The resulting wet-mixture was then sifted as in Example 5, dried to a moisture content of 1.33% (w/w) and compressed as

in Example 5.

The tablets had a hardness value of 10 kg (Monsanto), a disintegration time of 5 mins. 30 secs. and a friability of 0.33%. The T_{50} and T_{80} were 29 mins. and > 60 mins. respectively.

Example 9

Allopurinol (1.0 kg), having a particle size of 34μm and Primojel (66.7 g) were mixed for 10 minutes. A granulating solution containing polyethylene glycol 6000 (60 g) and purified water (110 g) was prepared.

The solution was wet-mixed with the powders for 10 minutes and subsequently sifted as in Example 5. The wet granules were dried to a moisture content of 0.51% (w/w) and then compressed as in Example 5.

The tablets had a hardness value of 5 kg (Monsanto), disintegration time of 3 mins. 15 secs. and a friability of 0.48%. The T_{50} and T_{80} values were 4 mins. and 9 mins. respectively.

Example 10

Allopurinol (5.0 kg), prepared as in Example 1, Primojel (83.4 g) were mixed in a Planetary mixer as in Example 2. A granulating solution containing gelatin (83.3 g), methyl hydroxybenzoate (2.5 g), purified water (416 g) and alcohol (300 g) 1 460 302 (6) BILL R. was prepared. The solution was wet-mixed with the powders for 15 minutes using a slow speed (14 rev/min.).

Granulation was carried out in a comminuting mill fitted with 0.6 cm screen and running at medium speed. The granules were subsequently dried in an oven on trays at 60°C for 12 hours to a moisture content of 0.32% (w/w) prior to sifting through a 1000μm screen. Magnesium stearate (50 g) sifted through a 250μm screen and Aerosil 200 (31.7 g) sifted through a 300μm screen were blended with the granules. The granules were compressed on a Manesty D3 Rotary Machine to provide tablets containing 300 mg allopurinol and having a hardness value of 8.8 kg (Monsanto), a disintegration time of 4 mins. 55 secs. and a friability value of less than 0.5%. The T_{50} and T_{80} Values were respectively 11 mins. and 22 mins. Each of the tablets weighed 315.05 mg and contained 300 mg of allopurinol.

The same granules were also compressed on a Manesty D3 Rotary Machine to provide tablets containing 100 mg allopurinol and having a hardness value of 4.0 kg (Monsanto), a disintegration time of 1 min. 47 secs., a friability value of less than 0.5%. The T_{50} and T_{80} Values were respectively 6 mins. and 14 mins. Each of the tablets weighed 105 mg and contained 100 mg of allopurinol.

WHAT WE CLAIM IS:—

1. A tablet formulation, which comprises from 80 to 98% (w/w) of allopurinol having a particle size, as herein before defined, from 2 to 40μm, from 1 to 19% (w/w) of a disintegrating agent and from 1 to 19% (w/w) of a granulating agent.

2. A tablet formulation according to claim 1, which comprises at least 85% (w/w) of allopurinol.

3. A tablet formulation according to claim 2, which comprises at least 90% (w/w) of allopurinol.

4. A tablet formulation according to claim 3, which comprises about 95% (w/w) of allopurinol.

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

6. A tablet formulation according to claim 5, which comprises about 2% (w/w) of a granulating agent.

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

8. A tablet formulation according to claim 7, which comprises about 2% (w/w) of a disintegrating agent.

9. A tablet formulation according to any one of the preceding claims, which is in the form of a tablet and which comprises from 250 to 350 mg of allopurinol.

10. A tablet formulation according to claim 9, which comprises about 300 mg of allopurinol.

11. A tablet formulation according to any one of claims 1 to 8, which is in the form of a tablet and which comprises from 50 to 150 mg of allopurinol.

12. A tablet formulation according to claim 11, which comprises about 100 mg of allopurinol.

13. A tablet formulation according to any one of the preceding claims, which comprises allopurinol having a particle size from 28 to 38μm.

14. A tablet formulation according to any one of claims 1 to 12, which comprises allopurinol having a particle size less than 28μm.

15. A tablet formulation according to claim 14, which comprises allopurinol having a particle size less than 15μm.

16. A tablet formulation according to claim 15, which comprises allopurinol having a particle size of about 10μm.

17. A tablet formulation according to any one of the preceding claims, wherein the disintegrating agent is sodium starch glycolate 18. A tablet formulation according to any one of the preceding claims, wherein the granulating agent is gelatin.

19. A method of preparing a tablet

in Example 5.

The tablets had a hardness value of 10 kg (Monsanto), a disintegration time of 5 mins. 30 secs. and a friability of 0.33%. The T_{50} and T_{80} were 29 mins. and > 60 mins. respectively.

Example 9

Allopurinol (1.0 kg), having a particle size of 34μm and Primojel (66.7 g) were mixed for 10 minutes. A granulating solution containing polyethylene glycol 6000 (60 g) and purified water (110 g) was prepared.

The solution was wet-mixed with the powders for 10 minutes and subsequently sifted as in Example 5. The wet granules were dried to a moisture content of 0.51% (w/w) and then compressed as in Example 5.

The tablets had a hardness value of 5 kg (Monsanto), disintegration time of 3 mins. 15 secs. and a friability of 0.48%. The T_{50} and T_{80} values were 4 mins. and 9 mins. respectively.

Example 10

Allopurinol (5.0 kg), prepared as in Example 1, Primojel (83.4 g) were mixed in a Planetary mixer as in Example 2. A granulating solution containing gelatin (83.3 g), methyl hydroxybenzoate (2.5 g), purified water (416 g) and alcohol (300 g) 1 460 302 (6) BILL R. was prepared. The solution was wet-mixed with the powders for 15 minutes using a slow speed (14 rev/min.).

Granulation was carried out in a comminuting mill fitted with 0.6 cm screen and running at medium speed. The granules were subsequently dried in an oven on trays at 60°C for 12 hours to a moisture content of 0.32% (w/w) prior to sifting through a 1000μm screen. Magnesium stearate (50 g) sifted through a 250μm screen and Aerosil 200 (31.7 g) sifted through a 300μm screen were blended with the granules. The granules were compressed on a Manesty D3 Rotary Machine to provide tablets containing 300 mg allopurinol and having a hardness value of 8.8 kg (Monsanto), a disintegration time of 4 mins. 55 secs. and a friability value of less than 0.5%. The T_{50} and T_{80} Values were respectively 11 mins. and 22 mins. Each of the tablets weighed 315.05 mg and contained 300 mg of allopurinol.

The same granules were also compressed on a Manesty D3 Rotary Machine to provide tablets containing 100 mg allopurinol and having a hardness value of 4.0 kg (Monsanto), a disintegration time of 1 min. 47 secs., a friability value of less than 0.5%. The T_{50} and T_{80} Values were respectively 6 mins. and 14 mins. Each of the tablets weighed 105 mg and contained 100 mg of allopurinol.

WHAT WE CLAIM IS:—

1. A tablet formulation, which comprises from 80 to 98% (w/w) of allopurinol having a particle size, as herein before defined, from 2 to 40μm, from 1 to 19% (w/w) of a disintegrating agent and from 1 to 19% (w/w) of a granulating agent.
2. A tablet formulation according to claim 1, which comprises at least 85% (w/w) of allopurinol.
3. A tablet formulation according to claim 2, which comprises at least 90% (w/w) of allopurinol.
4. A tablet formulation according to claim 3, which comprises about 95% (w/w) of allopurinol.
5. A tablet formulation according to any one of the preceding claims, which comprises less than 5% (w/w) of a granulating agent.
6. A tablet formulation according to claim 5, which comprises about 2% (w/w) of a granulating agent.
7. A tablet formulation according to any one of the preceding claims, which comprises less than 5% (w/w) of a disintegrating agent.
8. A tablet formulation according to claim 7, which comprises about 2% (w/w) of a disintegrating agent.
9. A tablet formulation according to any one of the preceding claims, which is in the form of a tablet and which comprises from 250 to 350 mg of allopurinol.
10. A tablet formulation according to claim 9, which comprises about 300 mg of allopurinol.
11. A tablet formulation according to any one of claims 1 to 8, which is in the form of a tablet and which comprises from 50 to 150 mg of allopurinol.
12. A tablet formulation according to claim 11, which comprises about 100 mg of allopurinol.
13. A tablet formulation according to any one of the preceding claims, which comprises allopurinol having a particle size from 28 to 38μm.
14. A tablet formulation according to any one of claims 1 to 12, which comprises allopurinol having a particle size less than 28μm.
15. A tablet formulation according to claim 14, which comprises allopurinol having a particle size less than 15μm.
16. A tablet formulation according to claim 15, which comprises allopurinol having a particle size of about 10μm.
17. A tablet formulation according to any one of the preceding claims, wherein the disintegrating agent is sodium starch glycolate 18. A tablet formulation according to any one of the preceding claims, wherein the granulating agent is gelatin.
19. A method of preparing a tablet

formulation according to any one of the preceding claims, which comprises admixing allopurinol, a disintegrating agent and a granulating agent.

20. A method of preparing a tablet, which comprises the compression on standard machinery of a formulation according to any one of claims 1 to 18.

21. A tablet formulation substantially as herein described and with reference to any one of Examples 1 to 10.

G. S. A. SZABO

Agent for the Applicants,
Chartered Patent Agent

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1976.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.