Convention Application for a Patent

We, DR. KARL THOMAE G.m.b.H., a Body Corporate organised under the laws of the Federal Republic of Germany,

of Biberach an der Riss, Federal Republic of Germany,

hereby apply for the grant of a Patent

for an invention entitled "NEW ORAL DIPYRIDAMOLE PREPARATIONS"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered P 31 24 090.9 for a patent or similar protection made in Federal Republic of Germany on 19th June, 1981.

Our address for service is: CALLINAN AND ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 18th day of June, 1982.

DR. KARL THOMAE G.m.b.H.

By its Patent Attorneys:

CALLINAN AND ASSOCIATES
DOCUMENTS LODGED WITH THIS APPLICATION ARE UNSUITABLE OR REPRODUCTION AND MAY BE INSPECTED AT THE PATENT OFFICE A.C.T.
Claim
1. Oral preparations in the form of granules, pellets or tablets containing dipyridamole, or a physiologically acceptable acid addition salt thereof, with a relative bioavailability of more than 100% (relative to dipyridamole solutions) and giving rise to substantially lower inter- and intra-individual blood dipyridamole level fluctuations containing at least 5 equivalents of orally acceptable acidic excipient per mole of dipyridamole or acid addition salt thereof, optionally together with conventional additives.
Australia

PATENTS ACT 1952

COMPLETE SPECIFICATION
(ORIGINAL)

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GERHARD BOZLER.

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48-50 Bridge Road, Richmond, State of Victoria, Australia.

Complete Specification for the invention entitled: "NEW ORAL DIPYRIDAMOLE PREPARATIONS"

The following statement is a full description of this invention, including the best method of performing it known to me—*

* Note: The description is to be typed in double spacing, pica type face, in a area not exceeding 250 mm in depth and 160 mm in width, on rough white paper of good quality and it is to be inserted inside this form.
New Oral Dipyridamole preparations

The invention relates to new oral preparations containing dipyridamole, or a physiologically acceptable acid addition salt thereof, with a relative bioavailability of over 100%, compared with dipyridamole solutions, and substantially lower inter- and intra-individual fluctuations in blood level. These new galenic preparations present particular advantages, in the pharmacokinetic respect, over the galenic forms known hitherto.

In the following description of the invention, references to dipyridamole are (unless the context requires otherwise) to be taken to include also physiologically acceptable acid addition salts thereof. The term "acid addition salts" includes salts formed by reaction of dipyridamole with organic or inorganic acids, for example hydrochloric, tartaric or citric acids.

Dipyridamole (2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidine) has been a valuable active substance for some years. The galenic preparations known hitherto which contain this active substance have a number of disadvantages, owing to the special physical properties of dipyridamole, for specific applications.

Since dipyridamole is readily water-soluble only in an acidic medium, it can only go into solution from solid galenic forms and then be resorbed if the galenic preparations remain in the acidic range for a sufficiently long period, i.e. the solubility and hence also the resorption depend greatly on the retention time and the pH value in the stomach and upper intestinal tract. This results in sharp inter- and intra-individual fluctuations in the blood levels (see Table 1), since the motility of the test subject and the pH of the patient's stomach and intestines and his food intake...
have a considerable influence on resorption. In a few patients, the blood levels may even be so low that they practically amount to an absence of resorption.

We have now devised a new, orally administered preparation which releases the active substance rapidly and, irrespective of the physiological conditions in the gastrointestinal tract (for example the pH, the buffering effect and the motility of this tract), results in a high, reproducible bioavailability of the dipyridamole.

Thus according to one feature of the present invention, there are provided oral preparations in the form of granules, pellets or tablets with a relative bioavailability of more than 100% (relative to dipyridamole solutions) and giving rise to substantially lower inter- and intra-individual blood dipyridamole level fluctuations containing at least 5 equivalents of orally acceptable acidic excipient per mole of dipyridamole or an acid addition -alt thereof optionally together with conventional additives.

In this respect, an acidic dipyridamole solution ought to be the best form of administration per se, since the active substance is given in dissolved form; one would expect total resorption together with a very high bioavailability. For this reason, it is usual to give the efficacy of a galenic preparation in terms of its relative bioavailability compared with a solution of the substance. For this purpose, the area under the blood level curve (= AUC) is determined and compared with that of the solution (= 100%). However, totally unexpectedly, it has been found that when the solid forms according to the invention are used, the relative bioavailability of dipyridamole is above the theoretically possible limit of 100%, namely 140-150%, by comparison with an acidic dipyridamole
an acidic solution, and another time orally as an acidic solution, lead to the conclusion that even when administered in dissolved form, dipyridamole is not resorbed totally, but only to about 60-70%.

This resorption quota can be determined not only from a comparison of the urine precipitation for both types of administration, but also from clearance calculations.

In the published British Patent Application No. 2039737A, Example 8 describes a granulate consisting of 0.5 kg of dipyridamole and 0.25 kg of fumaric acid and the preparation thereof. One mole of dipyridamole is used to four equivalents of fumaric acid. When this Example was followed, a dipyridamole granulate was obtained whose pH-independent solubility was totally unsatisfactory even though the fumaric acid was present in an excess of one mole of dipyridamole to four equivalents of fumaric acid. As can also be seen from Fig. 2 of the above application, the release of active substance is only 10% after one hour and only reaches about 100% after 6 hours. This, and the method of production described therein, show that this is a delayed release dipyridamole form.

We have now found, surprisingly, that dipyridamole preparations containing a mixture of dipyridamole or an acid addition salt thereof and one or more physiologically acceptable acidic substances in the ratio of at least 5 equivalents of acidic exipient per mole of dipyridamole or an acid addition salt thereof, preferably in an intimate mixture, result in highly reproducible blood levels with maximum bioavailability, only about 30 minutes to 2 hours after administration. This significant increase in the bioavailability of the dipyridamole was entirely unexpected.

The dependency of the solubility or speed of dissolution of dipyridamole on the quantity of acid added thereto was then investigated for different dosages using the example of film-coated dipyridamole tablets containing different added amounts of tartaric acid or fumaric acid per tablet. The tablets were tested in vitro using the USP-XX-paddle method at 100 rpm in 500 ml of dilute McIlvain buffer with a pH of 6.
Speed of release in vitro from dipyridamole film-coated tablets containing different added amounts of fumaric acid in a dilute buffer solution of pH 6 (75 mg of dipyridamole per tablet)

<table>
<thead>
<tr>
<th>Minutes</th>
<th>0 mg</th>
<th>30 mg</th>
<th>60 mg</th>
<th>120 mg</th>
<th>180 mg fumaric acid per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7</td>
<td>17</td>
<td>37</td>
<td>53</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>27</td>
<td>60</td>
<td>77</td>
<td>85</td>
</tr>
</tbody>
</table>

Speed of release in vitro from dipyridamole film-coated tablets with different added amounts of tartaric acid in a dilute buffer solution of pH 6 (75 mg of dipyridamole per tablet)

<table>
<thead>
<tr>
<th>Minutes</th>
<th>0 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
<th>40 mg</th>
<th>80 mg tartaric acid per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7</td>
<td>13</td>
<td>21</td>
<td>35</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>13</td>
<td>21</td>
<td>40</td>
<td>50</td>
<td>68</td>
</tr>
</tbody>
</table>
Speed of release in vitro from dipyridamole film-coated added amounts of fumaric acid in a dilute buffer solution per tablet:

<table>
<thead>
<tr>
<th>Minutes</th>
<th>% of dipyridamole released after the</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 mg</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

Speed of release in vitro from dipyridamole film-coated added amounts of tartaric acid in a dilute buffer solution per tablet:

<table>
<thead>
<tr>
<th>Minutes</th>
<th>% of dipyridamole released after the</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 mg</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
</tr>
</tbody>
</table>
Tablets containing different additions of pH 6 (75 mg of dipyridamole or 0 mg fumaric acid per tablet)

<table>
<thead>
<tr>
<th></th>
<th>66</th>
<th>85</th>
</tr>
</thead>
</table>

Tablets with different additions of pH 6 (75 mg of 80 mg tartaric acid per tablet)

|                | 39 | 68 |
It was not foreseeable that dipyridamole, which was present in relatively small absolute quantities and was totally dissolved, should form strongly supersaturated solutions with a concentration up to 20 times the saturation concentration, and that this phenomenon should occur particularly if there are present more than 5 equivalents of an acidic substance per mole of dipyridamole. In vivo tests with the new forms according to the invention (see Figures 1 and 2) show that a relative bioavailability of about 150% (relative to acidic solution) can be achieved when the forms according to the invention are used. A further advantage of these forms is that, owing to the pH-independent solubility, the release profile and hence also the blood levels can be controlled without any loss in bioavailability.

The extremely surprising discovery of the increase in relative bioavailability to about 150% (relative to solution) may possibly arise from the fact that supersaturated and more highly concentrated solutions of active substance are formed. When dipyridamole is administered in dissolved form, it is not impossible that some of the active substance might precipitate out of the solution in the upper section of the intestines, before being completely resorbed, which, surprisingly, would appear not to happen with supersaturated solutions. It must be borne in mind that, during the transition from the acidic stomach to the intestines, the solubility of the dipyridamole decreases by a factor of far more than 1,000 and, at pH 7.0 for example, it is only about 1 mg per litre. From about pH 4.0, the solubility of the dipyridamole is so low as to give virtually no levels of dipyridamole in the blood.

Since dipyridamole is a substance with a reversible effect, i.e. its therapeutic effect lasts only as long as the blood levels are kept sufficiently high, this results in a further improvement in the therapeutic activity. Thus, in general, the new galenic forms
accordings to the invention have the following advantages over conventional preparations:

1. Higher bioavailability
2. Higher therapeutic reliability, which is achieved by the fact that, on the one hand, the inter-
    and intra-individual fluctuations which are typical of known forms are reduced and, on
    the other hand, totally ineffective blood level values are avoided (for example in patients
    who normally only very slightly resorb dipyridamole, see Figure 3).
3. By controlling the release, it is possible to improve the therapeutic effect and avoid
    side-effects at higher doses (see Figure 2).
4. In some cases the higher bioavailability makes it possible to reduce the dosage (Figure 4
    shows that a reduction of the dose to 50 mg still yields a bioequivalent form).

It has been found that the remarkable increase in the relative bioavailability of the dipyridamole

20 can be achieved with a variety of pharmaceutical forms for oral administration. The essential prerequisite

for the high blood levels is the choice and correct ratio of acidic excipient to dipyridamole.

25 Extensive tests have shown that at least 5 equivalents of acidic excipient are required per mole of dipyridamole in order to obtain a significant improvement in the bioavailability of the dipyridamole. The quantity of acidic excipient in relation to the

dipyridamole has no upper limit per se; it is only limited by the fact that, if the quantity is too

30 great, it is not possible to produce an oral form of dipyridamole which can easily be swallowed. A

ratio of from 10 to 30 equivalents of acidic excipient

per mole of dipyridamole is preferred. Substances

suitable as the acidic excipient include a number of pharmaceutically acceptable organic edible acids

and organic and inorganic salts, for example citric,
Advantages

The surprising ease with which optimum solid dipyridamole preparations for oral administration can be produced was not foreseeable.

The dipyridamole forms of the present invention may, for example, be prepared according to the following processes, which processes constitute further features of the present invention:

Mixing together dipyridamole or an acid addition salt thereof and the acid excipient used, with or without binders and then compressing the mixture by means of tablet presses or roller compactors. The compressed mass is then broken up using dry granulating equipment and transferred into hard gelatine capsules. The quantity and nature of the acid excipient and the range of particle sizes in the dry granulate are critical in achieving optimum blood levels; or alternatively, dipyridamole or an acid addition salt thereof and the acid excipient used may be pelleted together, and the pellets with a diameter of from 0.1 to 2.0 mm (preferably from 0.5 to 1.0 mm) sorted out and transferred into hard gelatine capsules.

The granules and pellets may optionally subsequently be coated with a coating which releases at least 90% of the active substance, spread over a period of 2 hours, in the gastrointestinal tract.

The active substance may optionally also be mixed with the acidic excipient and other additives.
which may be used directly in tablets and with lubricant to form a mixture which can be made directly into tablets; this mixture is then compressed to form tablet cores which are subsequently covered with a lacquer or coating to mask the flavour.

The active substance may also first be granulated with one or more acidic substances in a moist or dry state, and after the addition of further excipients, the granules compressed to form tablet cores. However, it is also possible to make the active substance and conventional excipients into a granulate first, by moist or dry granulation, and then subsequently add the acidic excipients and a lubricant; only then is the mass compressed to form tablet cores.

Fumaric acid has proved a particularly suitable acid. It is physiologically completely harmless, easy to compress and, when combined with dipyridamole, does not produce a hygroscopic mixture. Its low solubility is essential to the invention; this ensures that, in the gastrointestinal tract, the particle of granulate is always surrounded by a sufficiently acidic microsphere in which the dipyridamole, which otherwise would not dissolve readily, is dissolved safely and completely.

If, for medical reasons, it is desirable to have a maximum blood level which is reduced in height but at the same time broader, there are a number of galenic possibilities. As can be seen from Examples 1 and 2, an increase in the amount of acid added leads to acceleration in the release of dipyridamole, whereas a reduction (Example 2) slows down the release of active substance.

Other possible forms of dipyridamole granulates are those where, besides readily water-soluble binders such as PVP, excipients which form a mucilage in the presence of water, or even water-repellent excipients, may be added to the dipyridamole and the acidic excipient.
As can be seen from the results of the release of active substance in Examples 3 and 4, there is sometimes a appreciable delay in the release of active substance of up to about 2 hours.

5 If, on the other hand, a very rapidly rising blood dipyridamole level is required, it is particularly advantageous to change the type of acid excipient used, as well as increasing the quantity of acid added or reducing the particle size of the granulate (enlarging the surface area). Owing to the high solubility of tartaric, citric, malic and ascorbic acids in particular, the dipyridamole dissolves completely in vitro in less than 5 minutes, irrespective of the pH of the medium of release (cf. Example 6).

10 Formulations of dipyridamole or an acid addition salt thereof and acid may also be produced in tablet form surprisingly easily. It has been found that, even in the presence of conventional tablet-making excipients, the compressing operation during tablet making is sufficient to achieve a sufficiently intimate mechanical combination of active substance and added acid. The Example relating to tablets (cf. the Tables on page 5) containing 40 or 80 mg of tartaric acid and 75 mg of dipyridamole (Example 10) illustrates this, as do Examples 11 and 12 which contain 60 and 120 mg, respectively, of fumaric acid, with the same content of active substance. For flavouring purposes, the tablets were all covered with a thin coating of hydroxypropylmethyl cellulose. To improve the handling qualities (and guard against hygroscopic behaviour), coated tartaric acid tablets were used in Example 10. Dissolution tests in vitro showed no significant differences between this product and non-coated tartaric acid. Without mentioning any further examples in detail, it is readily apparent to anyone skilled in the art that, owing to the nature and quantity of excipients added, the nature and quantity of acid excipient and the method of preparation (particle
The size of granulate), the release of the dipyridamole active substance can be controlled within a wide range of values to suit the medical requirements. Thus, in addition to the excipients polyvinylpyrrolidone, hydrogenated castor oil and polyacrylic acid, it is also possible to use excipients such as methyl-, ethyl-, hydroxyethyl- or hydroxypropylmethylcellulose. Furthermore, in order to achieve the desired release, the mixtures consisting of dipyridamole and acidic substances may be granulated with fats dissolved in organic solvents or with lacquers resistant to gastric juices such as cellulose acetate phthalate, shellac and hydroxypropylmethyl cellulose phthalate, and then be compressed and broken up again into granules.

If, for therapeutic reasons, higher dosages of dipyridamole are required and high blood level peaks should be avoided because of possible side effects, these requirements are met, according to the invention, by the forms described in Examples 8 and 9. At dosages of more than 100 mg of dipyridamole, for example, these forms produce a broadening of the maximum blood level, instead of reaching very high blood level peaks. Since these forms release the active substance in controlled manner, e.g. over a period of between 1 and 2.0 hours, the small particles are already located to a great extent in the duodenum, i.e. at a pH of over 4.0.

Therefore, these forms have to release the active substance in a pH medium in which the active substance is virtually biologically insoluble. If the release of dipyridamole is delayed any longer, i.e. if the small units of dipyridamole pass into lower sections of the intestines, there is no longer any guarantee of total dissolution and resorption.

The optimum resorption of dipyridamole is achieved, according to the invention, by accurately adapting the correlations between the nature and quantity of acidic excipient, the nature of the additives...
and the method of processing to the release of active substance required.

In vivo testing of the forms according to the invention in man:

All the tests were made on healthy volunteers, mostly in the form of cross-over tests. Since dipyridamole is only excreted in the urine to a very small extent, the only biological parameter used was the plasma level, which was determined by measurement of fluorescence. The galenic forms in Examples 1, 6, 8, 10, 11 and 12 were tested in man.

However, since the new oral preparations according to the invention without delayed release do not differ significantly from one another, the accompanying Figures 1 to 4 show only the results of in vivo tests on the forms described in Examples 1, 6 and 8.

Figure 1 shows the plasma levels of 12 test subjects after the administration of 75 mg of dipyridamole solution, by comparison with a capsule according to Example 1. It is found that after a short lag time which is presumably caused by the dissolution of the capsule substantially higher values are obtained, on average, with the new forms.

Figure 2 shows that, with controlled release, the maximum blood levels are only slightly higher than with the current commercial forms. However, this maximum value is maintained for a considerably longer period, i.e. dipyridamole may have a substantially longer lasting therapeutic effect in these forms without any increase in the risk of side effects.

A study of the plasma levels of the individual test subjects shows that, particularly with low values for the commercial forms and in the "non-absorbers" who occur from time to time, there is a very sharp increase in the plasma level (see Fig. 3) whereas, in test subjects who show a good plasma level with the commercial forms, there is only a relatively
small increase. Consequently, the usual fluctuations in plasma level which make therapy difficult are reduced significantly. This is also shown by a comparison of the variation coefficients of the standard commercial form and the form according to the invention in Table 1 below. With the exception of the values after 0.25 hours (this value being determined by the dissolving of the capsule), the variation coefficients of the new forms are about 60% lower.

**Table 1**

Comparison of the variation coefficients of the standard commercial forms and the new form:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Variation coefficients</th>
<th>(Standard through mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>commercial form</td>
<td>new form</td>
</tr>
<tr>
<td>0.25</td>
<td>92.4</td>
<td>141.1</td>
</tr>
<tr>
<td>0.50</td>
<td>120.9</td>
<td>45.0</td>
</tr>
<tr>
<td>0.75</td>
<td>63.2</td>
<td>15.8</td>
</tr>
<tr>
<td>1.00</td>
<td>59.6</td>
<td>17.0</td>
</tr>
<tr>
<td>1.33</td>
<td>58.1</td>
<td>18.5</td>
</tr>
<tr>
<td>1.83</td>
<td>54.7</td>
<td>20.7</td>
</tr>
<tr>
<td>2.33</td>
<td>55.4</td>
<td>23.3</td>
</tr>
<tr>
<td>3.00</td>
<td>50.6</td>
<td>31.0</td>
</tr>
<tr>
<td>4.00</td>
<td>60.6</td>
<td>31.0</td>
</tr>
<tr>
<td>5.50</td>
<td>61.4</td>
<td>43.6</td>
</tr>
<tr>
<td>8.00</td>
<td>61.6</td>
<td>28.1</td>
</tr>
</tbody>
</table>

Figure 4 shows that, with the new forms, plasma levels corresponding to those of the current commercial form are obtained with a reduction in dosage from 75 mg to 50 mg, i.e. a 33% reduction.
In the drawings:

MCG/ML = micrograms per millilitre
MG = milligrams

The following Examples are intended to illustrate the invention:
Tests with radioactively labelled dipyridamole where the substance was given once intravenously as

Example 1

3 kg of dipyridamole are mixed with 6.3 kg of fumaric acid and the mixture is moistened with 2 kg of a 15% alcoholic polyvinylpyrrolidone solution. After drying at 40°C and screening, the granulate is mixed with 300 g of polyvinylpyrrolidone powder and 100 g of magnesium stearate. The mixture compressed to form large tablets is broken up in a dry granulating apparatus and screened. The fraction of granulate measuring from 0.4 to 1.0 mm is used, and is transferred into hard gelatine capsules.

**In vitro release of the active substance dipyridamole:**

Conditions: USP XX-paddle method, 100 revolutions per minute at 37°C (unless otherwise stated, the in vitro release always occurred under these conditions)

<table>
<thead>
<tr>
<th>pH</th>
<th>USP gastric juice</th>
<th>McIlvain buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weight: 75 mg (based on dipyridamole);

<table>
<thead>
<tr>
<th>pH value</th>
<th>50%</th>
<th>&gt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>3 min.</td>
<td>8 min.</td>
</tr>
<tr>
<td>4.0</td>
<td>4 min.</td>
<td>12 min.</td>
</tr>
<tr>
<td>6.0</td>
<td>5 min.</td>
<td>15 min.</td>
</tr>
</tbody>
</table>

Example 2

45 kg of dipyridamole, 45 kg of fumaric acid and 9 kg of polyvinyl pyrrolidone are mixed for 20 minutes in a cube mixer. 0.5 kg of magnesium stearate are added and the mixture is agitated for a further 5 minutes. The mixture is then passed over a roller
tested in vitro using the USP-XX-paddle method at 100 rpm in 500 ml of dilute McIlvain buffer with a pH of 6.

compactor, behind which is connected a dry granulating apparatus with screening device. The fraction from 0.4 to 1.0 mm is used. Any finer particles are recycled and compressed again.

The granulate is transferred, in the required dosage, into suitable hard gelatine capsules.

Release of active substance dipyridamole:

<table>
<thead>
<tr>
<th>pH value</th>
<th>50%</th>
<th>&gt; 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>6 min.</td>
<td>12 min.</td>
</tr>
<tr>
<td>4.0</td>
<td>7 min.</td>
<td>20 min.</td>
</tr>
<tr>
<td>6.0</td>
<td>7 min.</td>
<td>25 min.</td>
</tr>
</tbody>
</table>

Example 3

30 kg of dipyridamole, 30 kg of fumaric acid, 29 kg of polyacrylic acid (brand name Carbopol 940) and 1 kg of magnesium stearate are made into a granulate exactly as described in Example 2.

Release of active substance dipyridamole:

<table>
<thead>
<tr>
<th>pH value</th>
<th>50%</th>
<th>&gt; 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>12 min</td>
<td>25 min.</td>
</tr>
<tr>
<td>4.0</td>
<td>15 min</td>
<td>40 min.</td>
</tr>
</tbody>
</table>

Example 4

2.5 kg of dipyridamole, 5.0 kg of fumaric acid, 1.3 kg of hydrogenated castor oil (brand name Cutina HR) and 0.1 kg of pyrogenic silicic acid (brand name Aerosil) are made into a granulate exactly as described in Example 1.
Release of active substance dipyridamole:

<table>
<thead>
<tr>
<th>pH value</th>
<th>50 %</th>
<th>75 %</th>
<th>&gt;90 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>28 min</td>
<td>65 min</td>
<td>105 min</td>
</tr>
<tr>
<td>4.0</td>
<td>34 min</td>
<td>72 min</td>
<td>123 min</td>
</tr>
</tbody>
</table>

**Example 5**

8.5 kg of dipyridamole are mixed with 9.0 kg of betaine hydrochloride and the mixture is moistened with 2.2 kg of a 10% isopropanolic polyvinylpyrrolidone solution. After drying at 40°C and screening, the granulate is mixed with 100 g of magnesium stearate and 230 g of pyrogenic silicic acid (Aerosil). The mixture is compressed to form tablets and broken up into granules; the fraction from 0.4 to 1.2 mm is used.

Release of active substance dipyridamole:

<table>
<thead>
<tr>
<th>pH value</th>
<th>50 %</th>
<th>&gt;90 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>5 min</td>
<td>9 min</td>
</tr>
<tr>
<td>4.0</td>
<td>7 min</td>
<td>14 min</td>
</tr>
</tbody>
</table>

Virtually identical values are obtained if betaine hydrochloride is replaced by sodium hydrogen sulphate.

**Example 6**

200 kg of tartaric acid in the form of spheroidal crystals with a particle size of between 0.5 and 0.8 mm are isolated in a rotary vessel with a 5% alcoholic solution of hydroxypropyl methyl cellulose. After moistening, in each case with a 10% alcoholic polyvinylpyrrolidone solution, a finely powdered...
mixture of
dipyridamole 8 parts
fumaric acid 2 parts

is sprinkled in until the pellets run free again.

After a short drying phase, adhesive solution is
sprayed in again and then further powder is added.
A total of 150 kg of the powder mixture are added
in this way, requiring about 75 kg of adhesive solution.
The pellets of active substance are between 0.6 and
0.9 mm in size and contain 33% of active substance
and 64% of organic acid. After the final application
of powder the pellets are thoroughly dried.
Release of active substance dipyridamole:

<table>
<thead>
<tr>
<th>pH value</th>
<th>50%</th>
<th>&gt; 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>2 min</td>
<td>3 min</td>
</tr>
<tr>
<td>4.0</td>
<td>2 min</td>
<td>3 min</td>
</tr>
<tr>
<td>6.0</td>
<td>2 min</td>
<td>4 min</td>
</tr>
</tbody>
</table>

As the starter cores it is also possible to
use small sugar pellets (nonpareils) or the following
acids or substances of acid reaction: citric, ascorbic,
malic or succinic acids, sodium hydrogen sulphate,
betaine hydrochloride, or the monosodium or potassium
salts of the above mentioned polybasic organic acids.

As the acidic component of the powder mixture
applied, it is possible to use not only fumaric acid
but all the abovementioned substances of acid reation,
7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9. The quantity of powder mixture to be applied to the starter may also be varied. However, care must be taken to ensure that the pellets contain at least 5 equivalents of acidic excipients to 1 mole of dipyridamole.

**Example 7**

In a fluidised bed granulator, 14 kg of dipyridamole, 0.5 kg of pyrogenic silicic acid (brand name Aerosil), 0.7 kg of corn starch, 2.5 kg of polyethyleneglycol powder 6000 and 25 kg of succinic acid are rotated at 70°C for 2 hours. After cooling, the mixture is passed through a 1.0 mm screen, 0.4% of magnesium stearate are added and the resulting mixture is transferred into hard gelatine capsules.

Release of active substance dipyridamole from hard gelatine capsules

<table>
<thead>
<tr>
<th>pH value</th>
<th>50 %</th>
<th>&gt;90 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>9 min</td>
<td>18 min</td>
</tr>
<tr>
<td>4.0</td>
<td>12 min</td>
<td>22 min</td>
</tr>
</tbody>
</table>

Instead of succinic acid it is also possible to use fumaric acid, sodium hydrogen sulphate and sodium hydrogen tartrate. The ratio of dipyridamole to acid or acidic salt may be kept within the limits specified by altering the composition of the mixture.

**Example 8**

1.9 kg of pellets of dipyridamole active substance according to Example 6 are sprayed with a 10% solution of hydroxypropylmethyl cellulose phthalate (brand name HP 55) in acetone/isopropanol 1:1 in a rapidly rotating coating vessel provided with baffle plates. Triacetin is added as the plasticiser:

The release of active substance at 4% by weight of the coating is as follows:
effect, i.e. its therapeutic effect lasts only as long as the blood levels are kept sufficiently high, this results in a further improvement in the therapeutic activity. Thus, in general, the new galenic forms

<table>
<thead>
<tr>
<th>pH value</th>
<th>25 %</th>
<th>50 %</th>
<th>75 %</th>
<th>90 %</th>
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</thead>
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<td>19 min</td>
<td>40 min</td>
<td>63 min</td>
<td>87 min</td>
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<tr>
<td>5.0</td>
<td>14 min</td>
<td>30 min</td>
<td>55 min</td>
<td>85 min</td>
</tr>
</tbody>
</table>

Example 9
A granulate is prepared from 5 kg of dipyridamole, 2.5 kg of polyethylene glycol powder 6000, 3 kg of fumaric acid, 2 kg of tartaric acid and 0.3 kg of pyrogenic silicic acid (brand name Aerosil). After screening, 0.2 kg of magnesium stearate are added and the mixture is compressed to form 10 mm biconvex cores weighing 260 mg, i.e. 100 mg of dipyridamole per core. After being thoroughly dusted, the cores are provided with a diffusion membrane in a coating pan. They are sprayed with a solution of Methacrylic acid - methacrylic acid ester copolymer (Eudragit S) and hydroxypropylmethyl cellulose phthalate (HP 55) in a ratio of 2:8 (acetone/isopropanol 1:1). In relation to the dry lacquer substance, 25% of polyethylene glycol 6000 are added as plasticiser and, if desired, coloured lacquer and talc are added.

With a coating content of 4% by weight, the following release data are obtained:

<table>
<thead>
<tr>
<th>pH value</th>
<th>25 %</th>
<th>50 %</th>
<th>75 %</th>
<th>90 %</th>
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<td>4.0</td>
<td>30 min</td>
<td>48 min</td>
<td>74 min</td>
<td>105 min</td>
</tr>
<tr>
<td>6.0</td>
<td>27 min</td>
<td>39 min</td>
<td>54 min</td>
<td>77 min</td>
</tr>
</tbody>
</table>
per mole of dipyridamole is preferred. Substances suitable as the acidic excipient include a number of pharmaceutically acceptable organic edible acids and organic and inorganic salts, for example citric,

Example 10
Film-coated tablets containing 80 mg of tartaric acid
per tablet
1 tablet contains:
5 Dipyridamole 75 mg - corresponding to 80 mg dipyridamole Tartaric acid 80 mg hydrochloride Tablet excipients ad 250 mg Preparation:
The active substance is made into an aqueous granulate with the tablet excipients, with the exception of the lubricant. To the finished granulate are added a lubricant and the tartaric acid coated with polyvinyl pyrrolidone and talc to produce the finished mixture ready for compressing. From this mixture, round biconvex tablets with a diameter of 8 mm are produced. To mask the taste, these are coated with hydroxypropylmethyl cellulose.

Example 11
Film-coated tablets containing 60 mg of fumaric acid
per tablet
1 tablet contains:
Dipyridamole 75 mg - corresponding to 80 mg dipyridamole Fumaric acid 60 mg hydrochloride Tablet excipients ad 195 mg Preparation:
The active substance is mixed with fumaric acid and granulated under moist conditions. To the finished granulate are added the remaining excipients which can be incorporated directly in tablets, to form the finished mixture ready for compressing. From this, round biconvex cores 8 mm in diameter are compressed and to mask the flavour these are coated with hydroxypropylmethyl cellulose in a coating vessel.
be released over a period of 2 hours, in the gastrointestinal tract. The active substance may optionally also be mixed with the acidic excipient and other additives.

Example 12
Film-coated dipyridamole tablets containing 120 mg of fumaric acid per tablet
1 tablet contains:
5 Dipyridamole 75 mg
5 Fumaric acid 120 mg
5 Tablet excipients ad 225 mg

Preparation:
Analogously to the film-coated dipyridamole tablets containing 60 mg of fumaric acid (Example 11).

Example 13
Film-coated dipyridamole tablets containing 60 mg of fumaric acid per tablet
1 tablet contains:
5 Dipyridamole 75.0 mg
5 Tablet excipients 60.0 mg
5 Fumaric acid 60.0 mg

Preparation:
Unlike in Example 11, dipyridamole is granulated with conventional tablet excipients. Fumaric acid and lubricant are added to the granulate to form the mixture ready for compressing. Further processing is effected analogously to Example 11.

Example 14
Film-coated dipyridamole tablets containing 60 mg of fumaric acid per tablet
1 tablet contains:
5 Dipyridamole 75.0 mg
5 Tablet excipients 60.0 mg
5 Fumaric acid 60.0 mg

Preparation:
As in Example 2, a dry granulate is prepared from 75 kg of dipyridamole, 60 kg of fumaric acid and 60 kg of excipients which can be incorporated directly in tablets (including polyvinyl pyrrolidone, magnesium stearate) to form a mixture ready for compressing. From this, cores with a diameter of 8.0 mm are compressed as in Example 11 and these cores are coated with a flavour-masking coating.
CLAIMS
The claims defining the invention are as follows:

1. Oral preparations in the form of granules, pellets or tablets containing dipyridamole, or a physiologically acceptable acid addition salt thereof, with a relative bioavailability of more than 100% (relative to dipyridamole solutions) and giving rise to substantially lower inter- and intra-individual blood dipyridamole level fluctuations containing at least 5 equivalents of orally acceptable acidic excipient per mole of dipyridamole or acid addition salt thereof, optionally together with conventional additives.

2. Oral preparations as claimed in claim 1 containing 10 to 30 equivalents of orally acceptable acidic excipient per mole of dipyridamole or an acid addition salt thereof.

3. Oral preparations as claimed in claim 1 containing 5 to 25 equivalents of orally acceptable acidic excipient per mole of dipyridamole or an acid addition salt thereof.

4. Oral preparations as claimed in any one of claims 1 to 3, wherein the acidic excipient used comprises one or more compounds selected from tartaric, citric, fumaric, succinic, malic, ascorbic and adipic acids, the acid sodium and potassium salts of these acids, sodium or potassium hydrogen sulphate, betaine hydrochloride, the anhydrides of succinic and glutaric acid which hydrolyse in water to form acids and D-glucuronic acid γ-lactone.

5. Oral preparations as claimed in any one of the preceding claims, wherein fumaric acid is present as the acidic excipient.

6. Oral preparations as claimed in any one of the preceding claims wherein dipyridamole or an acid addition salt thereof, intimately mixed with acidic excipient, is present in the form of granules with a particle size of between 0.1 and 2.0 mm diameter and the granules are optionally encapsulated into hard gelatine capsules.
35 The optimum resorption of dipyridamole is achieved, according to the invention, by accurately adapting the correlations between the nature and quantity of acidic excipient, the nature of the additives

7. Oral preparations as claimed in claim 6 wherein the particle size of the granules is between 0.25 and 1.25 mm diameter.

8. Oral preparations as claimed in any one of claims 1 to 5 wherein dipyridamole or an acid addition salt thereof, mixed with acidic excipient, is present in the form of pellets with a diameter of from 0.1 to 2.0 mm, and the pellets are optionally packed into hard gelatine capsules.

9. Oral preparations as claimed in claim 8 wherein the pellet size is from 0.5 to 1.5 mm diameter.

10. Oral preparations as claimed in any one of the preceding claims, wherein water-soluble binders and/or mucilaginous excipients and/or water-repellent excipients are also present.

11. Oral preparations as claimed in claim 10, wherein the additional binders and/or excipients are selected from methyl-, ethyl-, hydroxyethyl- or hydroxypropylmethylcellulose or polyacrylic acids or fats.

12. Oral preparations as claimed in any one of the preceding claims prepared by mixing dipyridamole or an acid addition salt thereof with one or more acidic excipients and other excipients which can be incorporated directly into tablets and with lubricant to form a mixture which can be made directly into tablets and then compressing the mixture to form tablet cores and coating them with a coating.

13. Oral preparations as claimed in any of claims 1 to 11 prepared by making dipyridamole or an acid addition salt thereof into a granulate by moist or dry granulation with one or more acidic excipients and, after the addition of further excipients, compressing this granulate to form cores and coating them with a coating.

14. Oral preparations as claimed in any one of claims 1 to 11, prepared by making dipyrimadole or an acid addition salt thereof into a granulate by moist or dry granulation with conventional excipients and,
after the addition of one or more acidic excipients and lubricant compressing this granulate to form cores which are then provided with a coating.

15. Oral preparations as claimed in any one of claims 12 to 14 wherein the coating is a flavour-masking coating.

16. Oral preparations as claimed in any one of claims 12 to 14 wherein the coating is a lacquer coating which can release at least 90% of the active substance in the gastrointestinal tract over a period of up to 2 hours.

17. Oral preparations as claimed in claim 6 or claim 7, wherein the granules are coated with a lacquer which can release at least 90% of the active substance in the gastrointestinal tract over a period of 2 hours.

18. Oral preparations as claimed in claim 8 or claim 9 wherein the pellets are coated with a lacquer which can release at least 90% of the active substance in the gastrointestinal tract over a period of 2 hours.

19. Oral preparations substantially as herein described.

20. Oral preparations substantially as herein described with reference to any one of the Examples.

21. Oral preparations as claimed in claim 3 substantially as herein described with reference to any one of Examples 1 and 3 to 12.

22. A process for the preparation of oral preparations as claimed in any one of the preceding claims wherein 1 mole of dipyridamole or an acid addition salt thereof is processed with at least 5 equivalents of orally acceptable acidic excipient, optionally together with conventional additives into pellets or granules, which are then filled or pressed into tablets.

23. A process for the preparation of oral preparations as claimed in any one of claims 1 to 21, as herein described.

24. A process for the preparation of oral preparations as claimed in any one of claims 1 to 21, as herein described with reference to any one of the Examples.
25. Oral preparations when prepared by a process as claimed in any one of claims 22 to 24.

DATED this 18th day of June, 1982.

DR. KARL THOMAE G.m.b.H.
By its Patent Attorneys:
CULLINAN AND ASSOCIATES
3.5 kg of polyvinyl pyrrolidone and 0.5 kg of magnesium stearate are added and the mixture is agitated for a further 5 minutes. The mixture is then passed over a roller.
Fig. 1

Plasma Level dipyridamole N =
0.8 mm are isolated in a rotary vessel with a 5% alcoholic solution of hydroxypropyl methyl cellulose.

After moistening, in each case with a 10% alcoholic polyvinylpyrrolidone solution, a finely powdered

Fig. 1

Plasma Level dipyridamole N=12

- = solution

■ = new form (Example 1)
The ratio of the mixture of dipyridamole and the acidic-reacting component which is to be applied to the cores may also have the following values, besides the above-mentioned value of 8:2: 10:0; 9:1:

Plasma level dipyridamole

- • = new form (Example 6)
- ■ = new form (Example 8)
- × = commercial form

Time (hours)

MCG/ML

0 0.5 1 1.5 2

0 1 2 3 4 5 6 7 8
Fig. 2

Plasma level dipyrid
Plasma level dipyridamole

- • = new form (Example 6)
- ■ = new form (Example 8)
- × = commercial form

**Fig. 2**

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<th>Time (hours)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
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<table>
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<th>Time (hours)</th>
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<th>3</th>
<th>4</th>
<th>5</th>
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- Table:

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<th>54 min</th>
<th>77 min</th>
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<td></td>
<td></td>
<td></td>
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</tbody>
</table>
and to mask the flavour these are coated with hydroxypropylmethyl cellulose in a coating vessel.

Fig. 3

Plasma level dipyridamole

Comparison of forms in individual test subjects

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>MCG/ML</th>
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<tbody>
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</tr>
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<td>2.5</td>
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<td>7</td>
<td>3.5</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

+ commercial form
• new form

+ commercial form
• new form

+ commercial form
• new form
Fig. 4

MCG/ML

Dipyridamole plasma level

various doses

○ = New form 75 mg, Example 6
■ = New form 50 mg, Example 6
□ = Commercial form coated tablet, 75 mg

Time (hours)
Fig. 4

Dipyridamole plasma levels after various doses
The size of particles is between 0.1 and 2.0 mm diameter and the granules are optionally encapsulated into hard gelatine capsules.

![Graph showing Dipyridamole plasma level vs. time for various doses.](image)

**Legend:**
- New form 75 mg, Example 6
- New form 50 mg, Example 6
- Commercial form coated tablet, 75 mg