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Dipyridamole sustained release formulations and processes for their preparation

This invention relates to new dipyridamole sustained release formulations and to processes for their preparation.

Dipyridamole [2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidine] is a pharmaceutically active substance which has been used successfully for many years. The nature of diseases which are treated with this active substance generally necessitate long-term treatment. At the present time in therapy, it is necessary for an instantaneous dipyridamole formulation to be administered three to four times a day since hitherto it has not been possible to formulate this active substance in an appropriate and effective sustained release form. A sustained release formulation would offer the following advantages in comparison with the present instantaneous formulations:

a) a reduction in the number of administrations per day means that the administration regime is more readily and easily complied with by patients. This is of especial importance in the case of long-term medication.

b) a delayed resorption leads to more uniform blood levels. Thus blood level peaks (which can lead to side effects) and sub-therapeutic levels as can occur with instantaneous forms especially in the case of relatively long intervals between administrations (e.g. during the night), are avoided. Hence the safety, compatibility and effectiveness of the preparation are increased.

Because of these obvious advantages of a sustained release form of dipyridamole there has hitherto been no shortage of attempts to realise such a formulation.

In the case of active substances which do not

already have "sustained release properties" per se (e.g. long biological half life, slow dissolving of crystalline active substances), such sustained release formulations can be obtained e.g. by the general following methods:

1. The active substance together with excipients is formulated so that it is released slowly, e.g. by embedding it in a matrix which does not dissolve or dissolves only slowly;

2. The active substance together with excipients is shaped into tablets or pellets, etc., which are then provided with an insoluble coating which results in a slow release of the active substance.

Furthermore, coating agents for solid medicaments are known (see German Patent Specification 2,415,490), which consist of a cellulose derivative soluble in the intestine and of a cellulose derivative insoluble in digestive fluids, these components being present respectively in a ratio of 30:70 to 70:30 by weight relative to one another. Also known are oral sustained release forms with a linear release of active substance in the gastro-intestinal tract (see German ALS 2,336,218), containing spheroidal medicament particles which are provided with a dialysis membrane whose film former comprises from 15 to 70% by weight of a cellulose ether which is insoluble in the pH range of the gastro-intestinal tract and which is not decomposable enzymatically, with an alkoxy group content of 43-50% by weight; and 85-30% by weight of one or more compounds containing in the molecule organic cellulose soluble only in the alkaline range of the intestinal tract, with a content of 5-40% by weight of free carboxyl groups such as e.g. hydroxypropylmethyl cellulose phthalate.

In general, the following prerequisites apply to an active substance for the development of a sustained

release formulation:
- good pH-independent solubility in the entire gastro-intestinal tract,
- no change in the resorption rate in the resorbable part of the gastro-intestinal tract.

However, the physical and biochemical properties of dipyridamole are completely unsuitable for the development of a conventional sustained release form. Thus:

a) the biological half life of dipyridamole is relatively short, that is existing blood levels drop quickly; a uniform dipyridamole blood level can be obtained only if active substance is constantly resorbed.

b) dipyridamole is soluble in aqueous medium only in acid pH range; above pH 4 this substance is practically insoluble in water. This means that dipyridamole can be dissolved and consequently resorbed only in the upper gastro-intestinal tract whereas at the higher pH values occurring in the intestinal region it remains insoluble and is not resorbed.

c) since the passage time through the stomach and the upper intestinal regions (with sufficiently acid pH) is relatively short (about 0.5 to 2 hours), it is difficult to maintain resorption over several hours. Moreover, the residence time in the stomach and in the various intestinal sections can vary considerably and thus, naturally, in the case of a substance whose solubility is pH-dependent, inter-individual and intra-individual blood level variations are extremely large when the formulation gives slow release of active substance, as is obtained with sustained release formulations.

d) even if dipyridamole is introduced dissolved into various intestinal sections, the resorption rate decreases from the duodenum to the colon.

For these reasons, those skilled in the art considered hitherto that the development of an effective sustained release of dipyridamole was not possible.

This is also indicated by the so-called "sustained release formulations" for dipyridamole presently known.

Thus, there is known, a so-called sustained release formulation based on the method (1) described above in which dipyridamole is pressed into matrix tablets with a swelling polyacrylic acid known by the brand name of Carbopol (RTM). The determination of release in vitro, however, shows that this is a completely unsuitable sustained release formulation of dipyridamole, since with this formulation dipyridamole can be dissolved only as long as the tablet is located in the acid medium of the stomach. When the matrix tablet reaches the small intestine, the release of active substance and consequently resorption practically cease. This is illustrated in Figs. 5 and 6 of the accompanying drawings wherein Fig. 5 shows the plasma levels of dipyridamole achieved in four test persons after administration of a formulation of the type described above including polyacrylic acid, each test subject receiving a dose of 2 x 200 mg of dipyridamole per day and, in Fig. 6 the dipyridamole level achieved by the fourth subject (GB) of Fig. 5 is compared with that achieved by administration to the same test subject of the same dose of dipyridamole in the form of formulations according to the invention described hereinafter. From Fig. 5 it will be noted that three of the test subjects exhibited dipyridamole levels which both in respect of relative bioavailability (calculated as the area under the curve) and of blood level maxima, are clearly complete therapy failures and at least 10% below those obtained with formulations according to the invention (cf. Fig. 6). The fourth subject (GB) had a rather higher blood level but still completely insufficient (relative bioavailability about 30%). The inadequate and sharply fluctuating blood levels obtained, however, make this hitherto known formulation totally unsuitable for use in therapy. On the other hand, the formulations according to

the invention result in a much more consistent and in general higher dipyridamole level. Furthermore the bioavialability is considerably increased.

French Patent Application No. 7528462 (based on method (2) described above) describes a recent sustained release formulation of dipyridamole in the form of pellets. The active substance is applied to inert starter cores which are subsequently provided with a sustained release coating. According to this publication pellets prepared according to the Eurand process (enclosing pellets within a polymer coating) are suitable for providing a dipyridamole sustained release preparation. However, as illustrated in Fig. 1 of the accompanying drawings, the blood levels of such dipyridamole sustained release pellets are distinctly lower initially than those obtained using undelayed commercial formulations and do not persist for any longer. Such formulations cannot therefore be considered as true sustained release formulations of dipyridamole, especially as the relative bioavailability in comparison with conventional coated tablets (i.e. instantaneous formulation) is impaired by about half.

Thus, Fig. 1 shows a plot of the level of dipyridamole in the blood as a mean value in an in vivo examination of 10 voluntary test persons against time after administration (a) of a conventional coated tablet, i.e. an instantaneous formulation, and (b) of a so-called sustained release formulation in the form of pellets prepared according to the Eurand process. Each formulation contained 100 mg of active substance. It was not possible to confirm in any way the blood level curve specified for one patient. As may be seen from this randomised cross-over comparison, the dipyridamole level obtained with the so-called sustained release pellets is distinctly lower (approximately half) initially than that obtained using the conventional instantaneous formulation and did not persist for any longer.

Thus, so-called sustained release formulations of dipyridamole known hitherto have proved to be completely unsuitable for use in therapy, although in the case of other active substances very useful sustained release formulations can be provided with the techniques employed. With these hitherto known so-called sustained release formulations, no dipyridamole is dissolved out of the preparation after entry into the small intestine as a result of the increase in pH. Thus resorption of the active substance ceases at this stage making it impossible to achieve the desired long-lasting blood levels.

We have now found that a dipyridamole sustained release formulation may, surprisingly, be prepared which allows for the special properties of dipyridamole, and substantially reduces or avoids the above-mentioned disadvantages of known sustained release formulations for dipyridamole. This new formulation permits a long-lasting dipyridamole blood level to be obtained by using a combination of different pharmaceutical techniques. Thus, we have found that:

1. The insolubility of dipyridamole at the higher pH values in the lower intestinal sections may be compensated for by the addition of acidifying substances.

2. Dipyridamole and acidifying substance may be incorporated within a membrane which prevents rapid neutralisation of the acidifying substance by the intestinal juices present in large excess and which holds back for a sufficiently long time the acidifying substance which dissolves much more quickly.

3. Particles may be formed from dipyridamole and acidic substances, surrounded by a membrane, which membrane exhibits release characteristics particularly adapted to dipyridamole.

Thus according to one feature of the present

invention there is provided a dipyridamole sustained release formulation comprising a plurality of spheroidal particles, each of the said spheroidal particles comprising:

a) a core containing dipyridamole or a salt thereof and a physiologically compatible acid substance in a ratio of at least 1 equivalent of acid substance to 1 mol of dipyridamole or salt thereof; and

b) a coating which surrounds the core, the coating comprising from 50 to 100% by weight of acid-insoluble lacquer soluble in intestinal juices and from 0 to 50% by weight of lacquer insoluble in gastric and intestinal juices, with the proviso that where the lacquer insoluble in gastric and intestinal juices comprises ethyl cellulose, the weight of ethyl cellulose present does not exceed 14% of the total weight of the coating. Preferably the coating will constitute from 3 to 30% of the total weight of the spheroidal particle.

This dipyridamole sustained release formulation according to the invention consists essentially of a series of spheroidal particles, which may be of equal or different particle size, each being composed of dipyridamole or of a salt, preferably a crystallised salt, of dipyridamole and an acid substance, e.g. one or more organic edible acids, in a ratio of at least 1 equivalent of acid substance to 1 mol of dipyridamole or salt thereof. If desired the acid proportion can be substantially higher than 1 equivalent per mol of dipyridamole or salt thereof, for example up to 30 equivalents, preferably 3 to 10 equivalents. The dialysis membrane surrounds the cores of the spheroidal particles and permits a pH-dependent control of dipyridamole release.

To produce the spheroidal particles, dipyridamole may, for example, be mixed and granulated with the acid substance, e.g. one or more organic edible acids such as citric acid or tartaric acid, in one of the ratios specified above. Optionally after the addition

of excipients such as lactose and magnesium stearate, the granulate can be pressed into curved cores with e.g. a diameter of 2 mm. The spheroidal particles can also, however, be present in the form of larger crystals with a spheroidal shape (e.g. when crystallised salts of dipyridamole are used), in the form of a rounded granulate or in the form of small beads (so-called pellets). Such forms are produced by processes known per se. Preferred are small pellets whose diameter is from 0.1 to 3 mm, preferably from 0.8 to 1.5 mm. Suitable as acidic substances are a plurality of toxicologically harmless acids such as e.g. fumaric acid, malic acid, tartaric acid, citric acid, succinic acid, ascorbic acid as well as acidic salts such as e.g. sodium or potassium hydrogen sulphate, betaine hydrochloride and the monosodium and monopotassium salts of tartaric acid and citric acid. Such acidic compounds may be used either alone or in admixture.

There may also be used acidic salts of dipyridamole in which case, it will be appreciated that the amount of a different acid substance present may optionally be less than 1 equivalent per mol of dipyridamole since the acidic salt of dipyridamole acts not only as a source of dipyridamole but also as an acidic substance. Such modified formulations according to the invention containing acidic dipyridamole salts form a further feature of the invention.

If desired, the core may comprise a central so-called "starter" core, preferably formed essentially from acidic substance and a bonding agent, to which is applied a powder mixture comprising the dipyridamole or salt thereof in admixture with acidic substance which may or may not be the same as that present in the "starter" core. Especially suitable for the "starter" cores are those acid substances which have an approximately spherical shape, e.g. tartaric acid, citric acid, malic acid, succinic acid, ascorbic acid, sodium or potassium hydrogen sulphate, monosodium

or monopotassium salts of polybasic acids or betaine hydrochloride.

The ratio of dipyridamole to acid substance must be selected so that the desired delayed release of dipyridamole is obtained. As will be appreciated release of the dipyridamole is also dependent on the type of coating used as discussed in more detail below.

As already mentioned above, the spheroidal particles may be produced by processes known per se, for example by means of a coating apparatus according to the Merumeriza process from acid substance and dipyridamole powder with the aid of bonding agents. The preparation may also be effected, for example, using a pelleting plate or a wet mixing appliance provided with special agitator arms. However, pellets are preferably produced by applying the active substance to "starter" cores which may either consist of conventional inert materials such as e.g. sugar or sugar alcohols, or else, as described above, may consist of the above-described acid substances in the presence of a bonding agent. The use of acid substances has two special advantages:

1. The dosage of dipyridamole in each of these sustained release formulations is preferably 150 to 250 mg. Since an approximately equal quantity by weight of acid substance is in general necessary, the combined weight of these two components is such that if they are to be introduced into an easily swallowable capsule, the dipyridamole plus acid substance component must make up 90 to 95% of the crude core. This is not possible when "starter" cores of inert material are used.

2. The use of a "starter" core formed from acid substance and which is then surrounded by a dipyridamole/acid substance mixture facilitates the otherwise

not easily attained complete release of dipyridamole.

Suitable bonding agents for use in forming "starter" cores include adhesive solutions such as e.g. starch paste, sugar syrup and solutions of gelatine, guar rubber, cellulose ether (e.g. methyl, ethyl, hydroxyethyl or hydroxypropylmethyl cellulose) or polyvinyl pyrrolidone. If desired a retarding lacquer layer may be provided between the "starter" core and the dipyridamole mixture.

In a preferred method for preparing the cores, rounded "starter" cores of tartaric acid with an average diameter of 0.3 to 1 mm, preferably 0.5 to 0.7 mm, are sprayed uniformly in a suitable vessel with an alcoholic polyvinyl pyrrolidone solution and then mixed with a mixture of by weight 80 parts of dipyridamole and 20 parts of tartaric acid until the cores roll freely again. After drying, this operation is repeated until the desired amount of active substance has been applied. The dipyridamole pellets thus obtained have, in general, a size of 0.9 to 1.2 mm and preferably consist, to the extent of at least 95% by weight, of active substance and acid in a ratio of 1.0 : 1.1. However, it is also possible to dissolve or suspend the active substance in adhesive solution and to apply this solution or suspension uniformly onto the surface of the "starter" cores.

Comprehensive in-vitro and in-vivo tests have shown that the composition of the coating is of particular importance. The coating applied to the cores should not dissolve in the resorbable part of the gastro-intestinal tract and must remain in the intestinal tract until substantially all the active substance is diffused out. The coating must hold back the acid substance situated in the core until the dipyridamole located therein is completely dissolved. If the coating is dissolved prematurely or becomes permeable, the intestinal juice present in large excess penetrates into the spheroidal particles and neutralises the acid substance present therein. Because of the virtual

insolubility of dipyridamole in the pH range of the intestine no more active substance can then be dissolved and resorbed. The acid substance present inside the particles and which dissolves in the fluid drawn into the particles dissolves, in turn, the dipyridamole and draws this through the membrane of the sustained release particles. Due to the increase in permeability of the coating in the intestinal tract, acid substance solution having dipyridamole dissolved therein is released in increasing amounts into the lower regions of the intestinal tract as the formulation progresses.

In vitro release tests with artificial intestinal juice of pH 6.0 to 7.0 show that the active substance dipyridamole diffuses out of the spheroidal particles even though it is practically insoluble above pH 4. Obviously, the intestinal juice is buffered by the acid substance upon penetration into the particles. Thus despite the intestinal juice, having a pH 6.0 to 7.0, which surrounds the sustained release formulation, an acid medium prevails within the particles as a result of which the dipyridamole can be dissolved and then diffused outwards in this dissolved form; dissolved resorbable dipyridamole is therefore released continuously into the intestinal tract. It was surprising and not foreseeable that dipyridamole released from the formulation remains resorbable in this form over a long time, although e.g. even micronised dipyridamole introduced into intestinal juice is not resorbed. Whilst not wishing to be limited by theoretical considerations it is believed the cause of this unexpected effect could either be a long-lasting over-saturation by dipyridamole of the intestinal juice, which may also be observed in vitro, or the dipyridamole precipitates with its molecules dispersed and is available for resorption in a finely divided form.

Since dissolved dipyridamole is resorbed especially quickly immediately after leaving the stomach in the uppermost intestinal section, which can lead

to high blood level peaks, while, on the other hand, the resorption rate decreases markedly in the lower intestinal sections, a sustained release coating is required which first delays release of the active substance and then releases it in an accelerated manner.

These criteria require a new type of dialysis membrane which is adapted specially to the unusual properties of dipyridamole and which permits a certain pH-dependent control of release. The composition of the coating used in the formulation according to the invention is selected so that it delays release in the pH range up to 4.5 and then exhibits an accelerating release of active substance as the pH value rises. The residence time of medicaments and the pH in the stomach and in the various intestinal sections differ sharply, however, from person to person and in one and the same person at different times. Too large a pH dependence of the release would therefore result in large differences in the blood level over time. However, if the total dose of active substance is divided into a large number, e.g. hundreds of independent small sustained release particles, then a statistically uniform, largely consistent passage of this sustained release formulation through the gastro-intestinal tract is possible. In this way the effects of differences in pH gradient and gastro-intestinal motility in individual patients on dipyridamole blood level behaviour are substantially compensated for. Thus to obtain the desired pH-dependent control of release in the case of dipyridamole it is necessary to use a plurality of spheroidal particles such as rounded granulates or pellets. This fact may be illustrated by an in vivo comparison of blood levels after administration of a small number of cores (diameter 6 mm) and of a large number of small pellets with the same coating type. Such a comparison is illustrated in Figs. 2 and 3 of the accompanying drawings. Thus Figs.

2 and 3 show the blood levels of dipyridamole achieved by administering formulations to six test subjects containing dipyridamole and acid substance in a ratio of 1:1. In Fig. 2 each formulation is in the form of several hundred pellets filled into a capsule. The dosage administered is 2x200 mg dipyridamole on the day preceding measurement followed by a further dose of 200 mg immediately prior to measurement commencing. In Fig. 3 each formulation is in the form of a capsule containing six large cores. The dosage administered is one dose of 200 mg of dipyridamole on the day of measurement. It will be noted that the blood levels achieved in Fig. 2 are much more uniform than those achieved in Fig. 3. Fig. 3 also illustrates the considerable difference in the blood levels of the same test person on different days. Furthermore, it may be seen that the substantially larger surface area in the case of the use of a large number of pellets as compared with the six cores leads to significantly higher and longer-lasting blood levels (cf. also Fig. 4, discussed in more detail below).

The dialysis membrane surrounding the individual particles largely consists (50 to 100% by weight) of acid-insoluble lacquer soluble in intestinal juice. Among others, coatings comprising from 50 to 90% by weight of a methacrylic acid/methacrylate copolymer (acid number 180-200), known by the brand name of Eudragit S, and 50-10% by weight of hydroxypropylmethyl cellulose phthalate, known by the brand name HP 55, have proved especially advantageous. Such a coating may, for example, be applied by spraying a 10 to 15% solution of both components on to the cores. Although such a coating consists only of components soluble in intestinal juice, surprisingly the coating does not dissolve in the resorbable part of the intestinal tract. The fact that such coatings are possible at all and are even especially suitable in this case is surprising for two reasons:

1. It is stated in DB-PS 2,415,490 that at least 30%, preferably at least 40% of the coating constituents

must be insoluble in acid and intestinal juice to produce a coating stable in intestinal juice.

2. It was not foreseeable that with such a high proportion of acid-insoluble lacquer a release takes place at all, since acid is constantly dissolved on the inside and is diffused through the membrane.

Suitable acid-insoluble lacquer components soluble in intestinal juice include e.g., in addition to those mentioned above, also cellulose acetate phthalate, ethyl cellulose phthalate, hydroxypropylmethyl cellulose succinate, cellulose acetate succinate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, hydroxypropylmethyl cellulose trimellitate and methacrylic acid/methacrylate copolymer (acid number 300 to 330, also known as Eudragit L), used either alone or in admixture.

A certain proportion of the lacquers soluble in intestinal juice can also be replaced by lacquers insoluble in the stomach and in the intestine, without the optimally acting sustained release formulation thereby suffering too much in its effect. Suitable as such lacquers are, in addition to ethyl cellulose, also lacquer substances based on acrylate or methacrylate, that is lacquers known by the brand name Eudragit retard S and Eudragit retard L. In this case, the lacquer components insoluble in gastric juice and in intestinal juice may be present in amounts up to 50%, preferably up to 30% by weight. Ethyl cellulose, however, may be used only in amounts of no more than 14% of the total weight of the coating.

As illustrated in Example 7 hereinafter, a release of dipyridamole which is first attenuated and then accelerates in lower sections of the intestinal tract can also be achieved by a successively formed coating. Thus, an initial coating consisting of 14% by weight of ethyl cellulose and 86% by weight of hydroxypropylmethyl cellulose phthalate can be sprayed with a coating consisting e.g. of cellulose acetate phthalate for further attenuation of the release of dipyridamole in the stomach and upper

intestinal tract.

If, however, the proportion of lacquer components soluble in intestinal juice is too small, that is if it drops below 50% by weight, then the release of dipyridamole from the sustained release particles is unsatisfactory as is illustrated hereinafter by in vitro tests (see also Examples 8 and 9) and tests in vivo which indicate a poor bioavailability (<70% relative to an instantaneous formulation). The cause of this poor release may be that the acid substance diffuses too quickly through the membrane. As a result no more active substance can be dissolved and diffused through the membrane owing to the insolubility of the dipyridamole in a non-acid medium. To correct this either the proportion of lacquer component soluble in intestinal juice must be increased or the acid "starter" core used in the production of the granulate or pellet is provided with a retarding lacquer layer by spraying it first with a solution of a lacquer component soluble in intestinal juice, for example with a solution of cellulose acetate phthalate or a lacquer combination of Eudragit retard S and Eudragit S (e.g. in a ratio of 1:1) and subsequently applying the dipyridamole to this retarded acid "starter" core.

The coatings mentioned according to the invention can, if desired, contain conventional excipients such as softeners, wetting agents and dyestuffs. Suitable are pharmacologically harmless softeners such as e.g. those from the series of glycerol phthalate, phosphate or citrate and polyethylene glycols, of which glycerol triacetate is preferred.

The dialysis membrane may be applied to the spheroidal medicament particles by methods known per se. Thus, for example, application can be effected in a rapidly rotating vessel or by the fluidised-bed process by spraying on the lacquer solution forming the dialysis membrane.

The dose of the active substance dipyridamole per formulation may, for example, be from 50 to 500 mg, but is preferably from 150 to 250 mg. The spheroidal particles prepared according to the above-described processes may, for example, be filled into hard gelatine capsules after they have been provided with the dialysis membrane. In so doing, it is possible to mix particles of different delay rates and also optionally to add undelayed active substance particles or pellets as a so-called starting dose. The dipyridamole sustained release particles can also, however, be mixed with pharmaceutical excipients and pressed into tablets. This is possible in the case of particles with a diameter no greater than 1.5 mm, preferably below 1 mm, without noticeably damaging the dialysis membrane. After being taken, such a tablet disintegrates in a few seconds and, like the capsules, releases the spheroidal dipyridamole particles.

The particular difficulty in selecting the optimal acid substance, the optimal quantity of acid substance, the optimal coating composition and the optimal coating thickness was that these four parameters cannot be varied independently of one another, but influence one another. It was thus not foreseeable to a person skilled in the art that a suitable sustained release preparation could be realised by this combination of different techniques. Thus it was necessary to overcome a number of problems each of which were inter-related. Thus we found:

a) It was possible to create a situation whereby dipyridamole becomes soluble independent of the pH of the gastro-intestinal tract.

b) A diffusion coating was found which protects the acid substance for hours against premature buffering by the intestinal juice present in large excess. The coating ensures that the

dissolved dipyridamole leaves the sustained release particles completely and the differences in dipyridamole resorption rates in the individual sections of the gastro-intestinal tract are compensated for by first a delayed release and then an accelerating release upon further penetration into the lower sections of the intestinal tract; the coating discovered brings about, therefore, a pH-dependent release instead of a linear release of the active substance.

c) Due to the distribution of the active substance in a large number of single sustained release doses, i.e. in the form of spheroidal particles, the effects of different residence times and of varying pH in the gastro-intestinal tract on the blood levels are equalised by statistical distribution of the rates of migration.

Fig. 4 shows a comparison of the blood levels achieved by administration (a) of a sustained release formulation according to the invention containing 220 mg of active substance and (b) of a conventional coated tablet (instantaneous formulations) containing 150 mg of active substance. It will be noted that, despite the higher dosage in the sustained release formulation a lower blood level maximum is achieved. Furthermore, with the sustained release formulation according to the invention the blood level is maintained at a high level over several hours. The bioavailability (calculated as the area under the curve) of the sustained release formulation according to the invention is from 90 to 110% (relative to the instantaneous formulation at the same dosage).

The following non-limiting Examples serve to illustrate the present invention. Throughout the Examples parts and percentages are expressed by weight

Example 1

200 kg of rounded tartaric acid "starter" cores of a particle size between 0.6 and 0.8 mm are moistened uniformly in a rotating vessel with a 10% alcoholic polyvinylpyrrolidone solution (lower alcohols are suitable for this purpose), whereafter a finely divided mixture of 8 parts dipyridamole and 2 parts tartaric acid is scattered therein until the pellets run freely again. After a short drying phase, adhesive solution is sprayed in again and further powder is then added. Altogether, 300 kg of the powder mixture are applied in this way, about 150 litres of adhesive solution being necessary. The active substance pellets obtained are between 0.9 and 1.2 mm in size and contain about 46% dipyridamole and 50% tartaric acid. The pellets are dried thoroughly after the final application of powder.

Example 2

200 kg of non-rounded citric acid "starter" cores with a particle size of 0.5 to 0.63 mm are coated, under exactly the same conditions as specified in Example 1, with 300 kg of a powdered mixture of dipyridamole and citric acid in a ratio 8:2 to a pellet size of 0.8 to 1.0 mm. The following acid substances were also used as "starter" cores (200 kg in each case): ascorbic acid, malic acid, succinic acid, sodium or potassium hydrogen sulphate, betain hydrochloride, monosodium or monopotassium salts of the above-mentioned polybasic organic acids. Used as acid component of the mixture of 8 parts of dipyridamole and 2 parts of acid applied are, in addition to tartaric acid or citric acid, likewise the above-mentioned acids and salts. Moreover, also mixtures of these compounds can be used as acid component. The ratio of the mixture of dipyridamole and acid substance which is to be applied to the cores can have, in addition to the above-mentioned value of

8:2 also the following values: 10:1, 9:1, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9. Moreover, in addition to 300 kg of the above-mentioned powder mixtures, the following quantities of the above-mentioned compositions can also be applied to 200 kg of starter cores: 100 kg, 200 kg, 400 kg, 500 kg, 600 kg. The active substance pellets thus prepared are between 0.7 and 1.5 mm in size. The ratio of dipyridamole to acid substance lies between 3:1 (600 kg of dipyridamole to 200 kg of "starter" cores) and 1:25.

Example 3

15 kg of dipyridamole powder are mixed with 17 kg of tartaric acid powder in a fluidised-bed granulating appliance. With slow spraying a structural granulate is produced by means of 25 kg of a 5% hydroxypropylmethyl cellulose solution (methylene chloride/isopropanol). 90% of the dried spherical granulate lies between 0.6 and 1.0 mm. The content of dipyridamole is about 45%. Instead of tartaric acid, also citric acid, ascorbic acid, fumaric acid, malic acid, succinic acid, monosodium and monopotassium salts of the above-mentioned polybasic acids, sodium or potassium hydrogen sulphate and betaine hydrochloride can be used. The content of dipyridamole can also have the following values by changing the composition of the mixture: 10%, 20%, 30%, 40%, 50%, 60%, 70%.

Example 4

19 kg of dipyridamole active substance pellets according to Examples 1 and 2 are sprayed in a rapidly rotating coating vessel with baffle plates with a solution of

Methacrylic acid/methacrylate copolymer (Eudragit S)	675 g
Hydroxypropylmethyl cellulose phthalate (HP 55)	675 g

in 8.5 kg of acetone/isopropanol 1:1. 150 g of triacetin

are added as softener. The release of active substance from the particles obtained is determined by the paddle method of USP XX (100 revolutions per minute). Unless otherwise stipulated, the release is always tested under the following conditions.

1 h	pH 2.0
1 h	pH 4.5
remainder	pH 6.0.

The buffering is effected with a saturated Na_2HPO_4 solution.

The following release values for dipyridamole are obtained:

1 h	5.0%
2 h	23.1%
3 h	48.0%
4 h	63.0%
5 h	75.1%
6 h	84.0%
7 h	89.0%

Example 4a

276 kg of dipyridamole active substance pellets according to Example 1 are sprayed in a rotating vessel intermittently with a solution of

Methacrylic acid/methacrylate copolymer (Eudragit S)	19.92 kg
Hydroxypropylmethyl cellulose phthalate (HP 55)	4.08 kg

in 300 kg of acetone/isopropanol (3:7). 8.16 kg of triacetin is added as softener and 4.08 kg of talcum as separating agent.

The following release values for dipyridamole

are obtained:
(Rotatmig basket method, USP XX, 100 revolutions per minute)
1 hour, pH 1.2 (USP gastric juice)
2 to 8 hours, pH 5.5 (phosphate buffer)

Time	dipyridamole released in %
1 h	5.1
2 h	22.9
3 h	42.7
4 h	54.9
5 h	64.7
6 h	74.2
7 h	82.7
8 h	90.6

Example 5

19 kg of dipyridamole active substance pellets according to Example 1 are sprayed in a fluidised-bed apparatus with a solution of

Ethyl cellulose (ethoxy group content 48-49.5%)	200 g
Copolymer of acrylates and methacrylates (Eudragit retard S)	100 g
Methacrylic/methacrylate copolymer (Eudragit S)	100 g
Hydroxypropylmethylcellulosephthalate (HP 55)	1,200 g

in 18 kg of acetone/ethanol 1:1. 400 g of triacetin are added as softener.

The following release values for dipyridamole are obtained:

1 h	2.9%
2 h	30.0%
3 h	77.6%

4 h 88.5%
5 h 93.0%

Example 6

19 kg of dipyridamole active substance pellets according to Example 1 are sprayed in a rapidly rotating coating vessel with baffle plates with a solution of

Copolymer of acrylates and methacrylates (Eudragit retard S)	200 g
Methacrylic acid/methacrylate polymer (Eudragit S)	200 g
Hydroxypropylmethyl cellulose phthalate (HP 55)	1,200 g

in 14 kg of acetone/isopropanol (1:1). 400 g of triacetin are added as softener.
The following release values for dipyridamole are obtained:

1 h 2.3%
2 h 14.3%
3 h 50.1%
4 h 70.8%
5 h 79.5%
6 h 88.2%
7 h 93.1%

Analogously, also the following composition were sprayed onto the pellets and granulates prepared according to Examples 1 to 3:

A) Methacrylic acid/methacrylate copolymer (Eudragit S) 80 parts
Triacetin 20 parts

B) Copolymer of acrylates and methacrylates (Eudragit retard S) 40 parts
Methacrylic acid/methacrylate copolymer

	(Eudragit S)	50 parts
	Polyethylene glycol 6000	10 parts
C)	Copolymer of acrylates and methacrylates	
	(Eudragit retard S)	20 parts
	Methacrylic acid/methacrylate copolymer	
	(Eudragit S)	70 parts
	Polyethylene glycol 6000	10 parts
D)	Methacrylic acid/methacrylate copolymer	
	(Eudragit S)	80 parts
	Methacrylic acid/methacrylate copolymer	
	(Eudragit L)	10 parts
	Triacetin	10 parts
E)	Cellulose acetate phthalate	60 parts
	Hydroxypropylmethyl cellulose phthalate	
	(HP 55)	30 parts
	Triacetin	10 parts
F)	Ethyl cellulose phthalate	70 parts
	Copolymer of acrylates and methacrylates	
	(Eudragit retard S)	20 parts
	Triacetin	10 parts
G)	Ethyl cellulose	10 parts
	Hydroxypropylmethyl cellulose	
	succinate	75 parts
	Triacetin	15 parts
H)	Hydroxypropylmethyl cellulose	
	trimellitate	35 parts
	Methacrylic acid/methacrylate copolymer	
	(Eudragit S)	60 parts
	Polyethylene glycol	5 parts

Example 7

2.0 kg of dipyridamole active substance pellets

according to Example 2 are sprayed in a rapidly rotating coating vessel with baffle plates with a solution of

Ethyl cellulose (ethoxy group content 48-49.5%) 28 g
Hydroxypropylmethyl cellulose phthalate (HP 55) 172 g
in 1.8 kg of acetone/ethanol 1:1.

The following release values for dipyridamole are obtained:

1 h	8.0%
2 h	28.1%
3 h	80.3%
4 h	90.3%
5 h	96.5%

It will be noted that the rate of release is initially rather rapid with approximately 80% release in 3 h. However, if these pellets are sprayed again with 80 g of cellulose acetate phthalate dissolved in 720 ml of acetone/isopropanol 1:4, the release is reduced to the following values:

1 h	4.1%
2 h	17.5%
3 h	35.7%
4 h	55.3%
5 h	65.6%
6 h	77.9%
7 h	86.3%
8 h	91.2%

Example 8 - formulation not according to the invention

2.0 kg of dipyridamole pellets according to Example 1 are sprayed in a rapidly rotating coating vessel with baffle plates with a solution of

Copolymer of acrylates and methacrylates

(Eudragit retard S) 200 g
Copolymer of acrylates and methacrylates
(Eudragit retard L) 100 g
in 2.7 kg of acetone/isopropanol 4:6. 30 g of dibutyl phthalate are added as softener.

The following release values for dipyridamole are obtained:

1 h	19.2%
2 h	38.7%
3 h	46.7%
4 h	49.0%
5 h	52.7%
6 h	54.1%
7 h	55.0%
8 h	55.1%

Example 9 - formulation not according to the invention

2.0 kg of dipyridamole pellets according to Example 1 are sprayed in a rapidly rotating coating vessel with baffle plates with a solution of
Copolymer of acrylates and methacrylates
(Eudragit retard S) 180 g
Methacrylic acid/methacrylic acid copolymer
(Eudragit L) 90 g
in 2.7 kg of acetone/isopropanol 1:1. 30 g of triacetin are added as softener.

The following release values for dipyridamole are obtained:

1 h	10.4%
2 h	22.5%
3 h	35.8%
4 h	45.1%
5 h	54.2%
6 h	61.1%
7 h	65.0%
8 h	67.2%

Example 10

a) 2.0 kg of rounded tartaric acid "starter" cores of a particle size of 0.6-0.8 mm are sprayed in a rotating vessel with a solution of

Methacrylic acid/methacrylate copolymer (Eudragit S) 35 g

Copolymer of acrylates and methacrylates (Eudragit retard S) 35 g

in 620 g of acetone/isopropanol 1:1. 10 g of triacetin are added as softener.

b) 2.0 kg of the coated tartaric acid "starter" cores according to Example 10a) are moistened uniformly in a rotating vessel with a 10% alcoholic polyvinylpyrrolidone solution. Thereafter, analogously to Example 1, 3 kg of a powdered mixture of 8 parts of dipyridamole and 2 parts of tartaric acid is added. 95% of the pellets lie between 0.9 and 1.25 mm, the content of dipyridamole being 45.6% and that of tartaric acid 50.2%.

c) 2.0 kg of dipyridamole pellets according to Example 10b) are sprayed in a rotating vessel with a solution of

Copolymer of acrylates and methacrylates (Eudragit retard S) 80 g

Methacrylic acid/methacrylate copolymer (Eudragit L) 100 g

in 1.8 kg of acetone/isopropanol 1:1. 20 g of Triacetin are added as softener.

The following release values for dipyridamole are obtained:

1 h	8.1%
2 h	27.3%
3 h	52.1%
4 h	64.7%
5 h	74.0%

6 h 81.7%
7 h 88.4%

Example 11

2 kg of coated dipyridamole pellets according to Example 4 with a dipyridamole content of 42.0% are mixed with 1.5 kg of microcrystalline cellulose, 0.4 kg of corn starch and 0.1 kg of polyvinylpyrrolidone. After the addition of 20 g of magnesium stearate, mixing is continued for a further 5 minutes. 718 mg of heavy oblong 7 x 13 mm tablets are pressed from the mixture with a weak applied pressure. The tablets disintegrate in about 45 seconds; the release of dipyridamole is accelerated only insignificantly.

Claims

1. A dipyridamole sustained release formulation comprising a plurality of spheroidal particles, each of the said spheroidal particles comprising:
(a) a core containing dipyridamole or a salt thereof and a physiologically compatible acid substance in a ratio of at least 1 equivalent of acid substance to 1 mol of dipyridamole or salt thereof; and
(b) a coating which surrounds the core, the coating comprising from 50 to 100% by weight of acid-insoluble lacquer soluble in intestinal juices and from 0 to 50% by weight of lacquer insoluble in gastric and intestinal juices, with the proviso that where the lacquer insoluble in gastric and intestinal juices comprises ethyl cellulose, the weight of ethyl cellulose present does not exceed 14% of the total weight of the coating.

2. A formulation as claimed in claim 1 wherein the coating constitutes from 3 to 30% of the total weight of each spheroidal particle.

3. A formulation as claimed in claim 1 or claim 2 wherein the core contains from 1 to 30 equivalents of acid substance per mol of dipyridamole or salt thereof.

4. A formulation as claimed in claim 3 wherein the core contains from 3 to 10 equivalents of acid substance per mol of dipyridamole or salt thereof.

5 A formulation as claimed in any preceding claim containing from 50 to 500 mg of active substance.

6. A formulation as claimed in claim 5 containing from 150 to 250 mg of active substance.

7. A modification of a formulation as claimed in any preceding claim wherein the core contains an acidic dipyridamole salt, said acidic dipyridamole salt constituting both a dipyridamole salt and an acid substance whereby the amount of a different acid substance present may be optionally less than 1 equivalent

per mol of dipyridamole.

8. A formulation as claimed in any preceding claim wherein the core is in the form of a sphere or pellet having a diameter of from 0.3 to 3 mm.

9. A formulation as claimed in claim 8 wherein the core is in the form of a pellet having a diameter of from 0.8 to 1.5 mm.

10. A formulation as claimed in any preceding claim wherein the acid substance comprises fumaric acid, malic acid, tartaric acid, citric acid, succinic acid, ascorbic acid, sodium hydrogen sulphate, potassium hydrogen sulphate, betaine hydrochloride, monosodium tartrate, monosodium citrate, monopotassium tartrate and/or monopotassium citrate.

11. A formulation as claimed in any preceding claim wherein the core comprises a central portion consisting essentially of physiologically compatible acid substance and a bonding agent, the said central portion being surrounded by a mixture of the dipyridamole or salt thereof and of physiologically compatible acid substance.

12. A formulation as claimed in claim 11 wherein a retarding lacquer layer is provided between the central portion and the dipyridamole mixture.

13. A formulation as claimed in any preceding claim wherein the acid-insoluble lacquer comprises methacrylic acid/methacrylate copolymer with an acid number of from 180 to 200, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, ethyl cellulose phthalate, hydroxypropylmethyl cellulose succinate, cellulose acetate succinate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, hydroxypropylmethyl cellulose trimellitate and/or methacrylic acid/methacrylate copolymer with an acid number of from 300 to 330.

14. A formulation as claimed in claim 13 wherein the coating comprises from 50 to 90% by weight of methacrylic acid/methacrylate copolymer with an acid number of from 180 to 200 and from 50 to 10% by weight

of hydroxypropylmethyl cellulose phthalate.

15. A formulation as claimed in any preceding claim wherein the coating contains a lacquer insoluble in gastric and intestinal juices.

16. A formulation as claimed in claim 15 wherein the coating comprises up to 30% by weight of lacquer insoluble in gastric and intestinal juices.

17. A formulation as claimed in claim 15 or claim 16 wherein the lacquer insoluble in gastric and intestinal juices comprises ethyl cellulose and/or acrylate- or methacrylate-based lacquers.

18. A formulation as claimed in any preceding claim wherein the spheroidal particles are each provided with a second coating consisting of a lacquer soluble in intestinal juices, the said second coating being applied over the coating which surrounds the core.

19. A formulation as claimed in any preceding claim wherein the spheroidal particles are contained within a hard gelatine capsule.

20. A formulation as claimed in any one of claims 1 to 18 wherein the spheroidal particles have a diameter no greater than 1.5 mm and, mixed with a pharmaceutical excipient, are in the form of a pressed tablet.

21. A formulation as claimed in any preceding claim wherein the core contains a crystallised dipyridamole salt.

22. A formulation as claimed in claim 1 substantially as herein described.

23. A formulation as claimed in claim 1 substantially as herein described in any one of Examples 4 to 7, 10 and 11.

24. A process for the preparation of a formulation as claimed in claim 1 which comprises forming a plurality of spheroidal cores containing dipyridamole or a salt thereof and a physiologically compatible acid substance in a ratio of at least 1 equivalent of acid substance to 1 mol of dipyridamole or salt thereof, and coating said cores with a coating whereby spheroidal

particles are obtained, the said coating comprising from 50 to 100% by weight of acid-insoluble lacquer soluble in intestinal juices and from 0 to 50% by weight of lacquer insoluble in gastric and intestinal juices, with the proviso that where the lacquer insoluble in gastric and intestinal juices comprises ethyl cellulose, the weight of ethyl cellulose present does not exceed 14% of the total weight of the coating.

25. A process as claimed in claim 24 wherein the coating is applied whereby it constitutes from 3 to 30% of the total weight of each spheroidal particle.

26. A process as claimed in claim 24 or claim 25 wherein the cores are formed by applying a mixture of dipyridamole or a salt thereof and of physiologically compatible acid substance to a central portion consisting of physiologically compatible acid substance and a bonding agent.

27. A process as claimed in any one of claims 24 to 26 wherein the cores are formed from a crystallised dipyridamole salt.

28. A process as claimed in any one of claims 24 to 27 for the preparation of a formulation as claimed in any one of claims 2 to 21.

29. A process for the preparation of a formulation as claimed in claim 1 substantially as herein described.

30. A process for the preparation of a formulation as claimed in claim 1 substantially as herein described in any one of Examples 4 to 7, 10 and 11.

31. A formulation as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 24 to 30.

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