Fig 95 14855

2196852

Case 100-6373 /III

NOVEL GALENICAL RETARD FORM

The invention relates to forms of pharmacologically active agents having controlled release properties and especially to solid dispersion forms of such agents having sustained release properties of the agent in an aqueous medium.

By incorporating an active agent in a solid dispersion or solution up till now merely an accelerated release was realized:
For example solid dispersion forms of medicaments are known, e.g. from the German Offenlegungsschrift Nr. 2.549.740, in which solid dispersions of griseofulvin in polyethylene glycol are described. The low dissolution rate and accordingly (see page 11, lines 4-5) the low bioavailability of griseofulvin were improved by the preparation of a solid dispersion of griseofulvin in polyethylene glycol. In the specifically described medicament formulation, a tablet, a disintegrant had to be added to the solid dispersion granulate since it appeared that a greatly improved dissolution rate of griseofulvin was again receded. The pressure applied in the production of tablets led to considerable cohesion between the tablet particles as a result of the strong cohesion between the polyethylene glycol molecules.

The disintegrant, crosslinked polyvinylpyrrolidone was added, in order to be able to re-form the original granulate particles of the tablet, in which the griseofulvin was present in a faster soluble form.

The water soluble polyethylene glycol, in contact with an aqueous medium, is extracted from the granulate by diffusion, the finely

divided griseofulvin coming into a situation to dissolve quickly.

According to the German Auslegeschrift No. 2.546.577 an increase of the dissolution rate and the resorption of salts of difficulty water soluble ergotamine compounds (especially of dihydroergotamine-methanesulfphonate, of dihydroergocristine-methanesulphonate, of dihydroergocryptine-methanesulphonate and of dihydroergocornine-methanesulphonate) is obtained when the salts are present in solid solutions in polyalkylene glycols and especially in polyvinylpyrrolidone of a molecular weight above 10.000. The mentioned drugs have in methanesulphonate salt form a water solubility above 0.01 % and are in this respect distinguished from the active agents used according to the invention.

According to the European application No. 78430 an increase of the dissolution rate and a maintenance of the resorption of dihydropyridines, especially of Nifedipine and of Nimodipine is obtained on dissolving these agents together with polyvinylpyrrolidone, e.g. having a molecular weight of 25.000, in a small quantity of a liquid organic solvent such, that the solid particles are only just dissolved after which this solution is mixed and granulated with solid carriers having a large capacity to absorbe, leading to evaporation of the organic solvent.

The drug is present in the solid polyvinylpyrrolidone in a dissolved state and shows on contact with an aqueous medium an increased dissolution rate. Both these features distinguish these known products from the compositions of the present invention.

According to the Canadian patent No. 987.588 an increase of the dissolution rate and of the bioavailability of difficulty water-soluble drugs is obtained when they are present as solid dis-

persions in polyethylene glycols and in other water-soluble matrix materials, e.g. pentaerythritol, pentaerythritol tetraacetate or citric acid.

The known drugs digitoxin 17-methyltestosterone, prednisolone acetate and hydrocortisone acetate are present at concentrations up to 5 % in the matrix material, thus giving dispersions which are different from the dispersions according to the present invention. The drug griseofulvin has, as indicated above, a water-solubility of more than 0.01 % and is therefore distinguished from the active agents used according to the invention.

We have discovered that if solid dispersions of pharmacologically active agents, practically insoluble in water are employed in such a matrix material, no significant expected increase of the dissolution rate in an aqueous medium is observed. Instead a decrease is obtained, without a material loss of bioavailability.

We have additionally discovered, that the decrease of the dissolution rate may be attributed to a coherent crystalline form of the drug, hereinafter referred to as a secondary structure, which form may be maintained even if the water-soluble matrix material is removed on contact with an aqueous medium, e.g. water.

To permit the secondary structure to be formed, it is preferred to have the drug in the solid dispersion present in a concentration above 5 %, and for more than 5 percent by weight in a crystalline form preferably as particles of a diameter below 5 micrometer and having a water-solubility up to 0.01 %, preferably below 0.005 percent by weight.

The present invention therefore relates to a solid dispersion of a pharmacologically active agent in a water-soluble crystalline matrix as a carrier, in which the active agent

a) has a maximum solubility of 0.01 % at 37°C in water,

b) is present in the matrix at a total concentration of above 5 percent by weight, and

c) is present in the matrix at a concentration of above 5 percent by weight in a coherent crystalline form.

This solid dispersion has in an aqueous medium a decreased dissolution rate. It is claimed in the parent application No. 84 14855.

A decreased dissolution rate was established in the following cases in the art:-

German Offenlegungsschrift No. 1.617.362 describes suspending pharmacologically active agents, particularly theophylline, in molten waxes for the preparation of galenical forms having a decreased dissolution rate in an aqueous medium. As a wax polyethylene glycol is used.

However, the solubility of theophylline is not low enough (above 0.01 %) and only the additional incorporation of conventional retardation excipients, like beeswax or stearic acid can cause a satisfactory decrease of the dissolution rate of the drug.

According to German Offenlegungsschrift No. 3.318.649 a two phasic solid pharmaceutical composition is described which contains crystalline Nifedipine and separately a solid solution of Nifedipine in a matrix material, particularly in polyvinylpyrrolidone. On contact with an aqueous medium, Nifedipine is dissolved from the

solid solution at an increased dissolution rate and from the solid Nifedipine crystals at a decreased dissolution rate.

According to the present invention only a solid dispersion of the drug is present, which on contact with an aqueous medium causes the release of the drug at a decreased rate.

The practically insoluble pharmacologically active agent in the dispersion according to the invention is 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester (compound B).

Information is also given herein on nifedipine, 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-ethoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid ethyl ester (hereinafter referred to as compound A), and (-)-(S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-1,2,6-trimethyl-3-pyridine carboxylic acid isopropylester (compound C). Compositions containing these compounds form no part of the invention, but the preparative examples and information thereon illustrate embodiments, techniques and/or results applicable to the present invention.

Dihydropyridines are extensively described in the literature and have particularly a calciumantagonistic activity. They are described e.g. as antihypertonics and as medicaments to treat angina pectoris.

The above-mentioned dihydropyridine is known, e.g. from the British patent No. 2,037,766.

It has been established, that the dihydropyridine is practically water-insoluble and thus has a water solubility of less than 0.01%.

Processing of it into a solid dispersion form however did not, as expected, result in an increased dissolution rate but surprisingly in a significantly decreased dissolution rate (see the comparative tests 1 to 5), advantageous in compositions which are to be administered once-a-day.

This retard effect is attributed to the solid dispersion, e.g. in granulate form, independent of optionally present excipients. An advantage is that no customary drug burst appears and that there is not significant decrease of the bioavailability (see the comparative tests).

The present invention thus provides a pharmaceutical composition for administration once-a-day, containing a therapeutical effective amount of the compound B. A similar composition containing compound A is claimed in the divisional application No. 87 27055. The matrix materials are preferably pharmaceutical acceptable solid compounds conventionally widely used as pharmaceutical excipients.

Since they must preferably be water-soluble, they should have polar properties. Most of these matrix materials thus have polar groups, e.g. oxy groups, especially hydroxy groups.

The preferred pharmaceutical compositions contain a solid dispersion of pharmacologically active agents in a polyalkylene glycol, particularly in a poly(C_{2-3})alkylene glycol, e.g. in a polyethylene glycol and are claimed generally in the parent application No. 85 14855.

The present invention in one aspect provides such a solid dispersion for compound B. A similar dispersion of compound A is claimed in the parallel divisional application No. 87 27055. The polyethylene glycol preferably has a molecular weight from 1000 to 20.000, especially from 4000 to 20.000, particularly from 4000 to 8000, e.g. 6000.

The solid dispersions may be obtained by dissolving the active agents at a concentration above 5 per cent by weight, in the liquified dispersing agent and solidifying the obtained mixture.

Liquifying the dispersing agent may occur by melting or by addition of a liquid organic solvent.

Solidifying of the liquid active agent containing dispersing agent may occur, e.g. by cooling or by evaporating the liquid organic solvent.

A process for the preparation of a solid dispersion of a pharmacologically active agent in a crystalline matrix as a carrier is performed in such a manner, that the active agent, having a maximum solubility of 0.01%, preferably below 0.005%, in water at 37°C, is dissolved at a concentration of above 5 per cent by weight in liquified matrix and the obtained mixture is transformed to a solid form and the active agent is crystallized.

After obtaining the solid dispersion it may be reduced to a conventional particle size, giving a granulate useful for further processing.

At least 5 percent of weight of the drug particles present in the solid dispersion are so small, that it is impossible to see them by conventional optical measurements, since if suspended for measurement purposes in an aqueous medium, they appear to have a Brownian perpetual motion.

Hence the particles are assumed generally to have a diameter of 5 micrometres or less.

Laserlight scattering tests in the aqueous suspension established a particle size of even less than 0.5 micrometer.

Comparison of the Guinier-de Wolff-spectra of the solid dispersion and of a corresponding mechanical mixture showed no significant difference.

The spectra show further that both drug and matrix material in the dispersion are in a crystalline form.

The concentration of the drug in the matrix may vary from 5 to 80 %, especially from 20 to 50 %, and particularly from 20 to 40 percent of weight and contributes to the sustained release effect according to the invention. (Greater concentration may cause a greater decrease of the dissolution rate, see curves 14 to 18 in fig. 5 for the dissolved quantity in percent of weight versus time T in hours; increasing concentrations of 10 to 50 percent by weight of compound A may cause a decrease of the dissolution rate).

Curves 14 to 18 in fig. 5 relate to solid dispersion granulates of the same subfraction, containing 10, 20, 30, 40 and 50 percent by weight of compound A .

The appropriate dose of the active agent amounts preferably up to 250 mg and preferably up to 200, especially up to 100 mg for compound A and up to 50, preferably up to 30, especially 10 to 25 mg for compound B per day. For a rationally administrable dispersion quantity a concentration from 10 to 80% of active agent in the matrix, on the average up to 50%, e.g. 40% of compound A and 20 percent by weight of compound B are indicated.

If the chemical stability of the active agent is not high, then the temperature of the molten matrix material, e.g. of the polyalkylene glycol, should be kept appropriately low. If more active agent is added to the polyalkylene glycol, then can be dissolved at the maximum allowable temperature; the excess will not be dissolved, but will be incorporated as a suspension.

The undissolved fraction particles preferably should have a particle size of at most 100 micrometres.

After cooling of the suspension these particles may be found in the dispersion with an similar size in addition to the fraction of active agent, that was dissolved and after cooling can be found again in the form of crystals having a diameter of at most 5 micrometres.

In the granulating process, briefly described above, the solid dispersion is preferably reduced to a particle size from 50 to 2000 micrometer, especially from 90 to 1000, mor particularly from 125 to 500 micrometer.

The particle size of the granulate contributes to the controlled release effect according to the invention (larger particles cause a greater decrease of the dissolution rate, see curves 19 to 22 in fig. 6; dissolved quantity in percent by weight versus time T; an increasing particle size causes a decrease of the dissolution rate, curves 19 to 22 relate to sieve factors of 90 to 180, of 180 to 355, of 355 to 500 and of 500 to 710 micrometre respectively of the dispersion granulate of a 40% dispersion of compound A in polyethylene glycol 6000.

Summarizing, it may be concluded that the release of the pharmacologically active agent can be controlled by changing the concentration of the active agent in the solid dispersion as well as by varying the particle size of the solid dispersion granulate.

Surprisingly, it has been established that when the dispersion granulate particles, e.g. those of Example 1, are brought into water, their matrix fraction is dissolved quickly and quantitatively. The active agent particles which in the dispersion have for example a size of up to 5 micrometre, form coherent secondary structures, their density and diameter varying according to the concentration of the active agent in the matrix and the diameter of the granulate particles.

A secondary active agent structure is thus formed from the solid dispersion after selective extraction of the matrix material, e.g. in an aqueous medium. This secondary structure may have a diameter comparable to that of the dispersion granulate. It shows in water a retarded dissolution rate. It can be partially restored to its original particles of up to 5 micrometre by intensive ultrasonic treatment.

Particles of active agent which in the dispersion granulate may have for example a diameter of up to 100 micrometre are in the secondary structure, which has been proceeded from the particles of up to 5 micrometre, enclosed in an unchanged state.

Since the original agent particles up to 5 micrometre and the additionally enclosed agent particles up to 100 micrometre contribute to the controlled release effect, both their solid dispersions and secondary active agent structures belong to the present invention.

The diameter and the surface of the secondary structure particles of the active agent have been investigated. They show irregular fissurelike channels and have an external and an internal surface.

Both the size and the structure of the external surface influence the dissolution rate in an, e.g. aqueous, solvent medium. The internal surface shows narrow pores up to 1 micrometre which hardly contribute to the release of active agent, since if they contain a solvent medium, its mobility is strongly reduced.

The size of the secondary structure corresponds to the size of the solid dispersion granulate particles, from which they originate.

After removal of the solvent medium, e.g. by drying, the specific surface and the pore volume are measurable.

The secondary structure of the active agent of a diameter of preferably from 50 to 2000, more particularly from 90 to 1000, especially from 125 to 500 micrometre. has a porous structure of a specific surface of 1 to 15 m^2/g, preferably from 2 to 12 m^2/g, measured according to the BET-method and by a pore volume of 20 to 95%, measured by mercury-porosimetry.

The solid dispersion particles as well as the secondary structure particles are usable for the preparation of pharmaceutical compounds.

The secondary structures are generally claimed in parent application No. 85 14855 and specifically for compound A in copending divisional application No. 87 27055.

The pharmaceutical compositions contain the solid dispersion granulate or the secondary structure particles.

Pharmaceutical compositions containing the solid dispersion granulate can be considered as galenical precursor forms of corresponding compositions containing the secondary structure particles, since their behaviour in the body is comparable with that of pro-drugs.

For the preparation of the pharmaceutical oral administration forms containing the solid dispersion, the granulate of the solid dispersion may be mixed in a conventional manner with suitable pharmaceutical excipients, e.g. a filling agent, such as lactose, a glidant, e.g. silicon dioxide and a lubricant, e.g. magnesium stearate (see. e.g. examples 2, 5 , 6 and 9) and optionally a desintegrant, such as crosslinked polyvinylpyrrolidone, e.g. crosspovidone (see. e.g. examples 2, 3, 5 and 6), or sodium carboxymethylcellulose (see example 9) and may be manufactured to conventional solid oral administration forms, such as tablets or capsules.

For the preparation of tablets the solid dispersion granulate may preferably be mixed with e.g. lactose, silicon, dioxide and magnesium stearate (see example 4, 5, 6 and 9).

The porous secondary structure agent particles are preferably used in capsules, since they are less able to resist the pressure for tabletting.

For the preparation of capsules, the solid dispersion granulate of the secondary structure agent particles may be mixed in conventional manner preferably with a placebo granulate from suitable excipients like lactose, starch and polyvinylpyrrolidone and with a mixture of crospovidone, silicone dioxide and magnesium stearate (see examples 2 and 3). The desintegrant may be used for suspending the capsule content.

Generally pharmaceutical administration forms, especially capsules and to a lower extent tablets as well show, during the passage through the stomach, a drug burst, which can to a large extent be prevented by applying an enteric coating on it. Suitable enteric coatings include hydroxypropylmethylcellulosephthalate (see example 3,5, 6 and 12). If the active agent is resorbed in the upper part of the intestines - dihydropyridines are such agents - then such a coating is very beneficial and does not impair the resorption process.

Tablets, which contain the components in compressed state, may need this coating to a lower extent, but then the desintegrant should be omitted (see the tablet of example 4, which contains no crosslinked polyvinylpyrrolidone).

We have established, that capsules or tablets without an enteric coating may be made if a hydrophobic excipient, such as a fatty acid glyceryl ester, is added to the solid dispersion (see examples 8 and 9 and comparative test No. 4). This hydro-

phobic ester reduces the drug burst in the stomach and may not significantly disturb the resorption process in the intestines. Such compositions may be prepared by dissolving the pharmacologically active agent in the liquid matrix and emulgating the obtained mixture with the hydrophobic substance, e.g. the fatty acid glyceryl ester, as much as possible, after which the obtained mixture may be solidified by cooling.

Preferred fatty acid glyceryl esters are physiologically acceptable esters, like (C_{10-20})fatty acid, e.g. palmitic and/or stearid acid glyceryl esters. These esters may be, e.g. mono-, di- and/or triesters of glycerin.

The amount of fat is preferably up to 60 percent of the total weight of the solid dispersion, e.g. 5 to 60%, and is particularly up to 15 to 25%, e.g. 20%.

The quantities of active agent to be administered may be dependent on various factors, e.g. the conditions to be treated, the duration of treatment desired and the rate of release of the active agent.

The amount of active agent required and the rate of release may be determined using in vivo techniques, e.g. measuring the concentration of active agent in the blood serum.

The pharmaceutical compositions of e.g. the compound B may be used e.g. for the same indications as described in the British patent No. 2037766.

For the antihypertonic use e.g. up to 50, especially up to 25, particularly 10 to 20 mg of compound B are used per day.

A pharmaceutical composition for plasma levels of 2 to 8 ng of compound A per ml during at least 22 hours, in the event that it contains one dosis of 50 mg of the active agent is claimed in the divisional application No. 87 27055. Basis for its behaviour are the plasma level curves 1,3,4,5 and 6 to 13 in fig. 1 to 4.

The present invention especially provides a pharmaceutical composition for plasma levels of 1 to 2,5 ng of compound B) per ml, during at least 22 hours, in the event that it contains one dosis of 10 mg of the active agent. Basis for this observation are the plasma level curves 23 and 26 in fig. 7 and 8.

The plasma level of compound A for curves 1 to 13 in fig. 1 to 4 (concentrations vs. time) may be determined gaschromatographically.

A plasma sample of 1 ml, adjusted with NaOH to pH 13, was extracted with toluene, the toluene was evaporated and the residue dissolved in 0.5 ml of toluene. 2 microlitres of the formed solution were separated at 300°C in a OV 17 column(6% on Gaschrom Q 100-120 mesh) using a argon/methane gas (95:5 volume/volume)mixture as a carrier gas(rate 60 ml/min). The analysis may be carried out using an electron capture detector. The retention time of compound A was 3.1 min.

The concentration of the compound was calculated by peak measurement in comparison to the peak of an internal standard. The detection limit is 0.5 ng of active agent per ml of plasma.

The dissolution rate of compound A in vitro for curves 14 to 22, of compound C in example 13 and of nifedipine in example 14 (dissolved quantities in percent by weight vs. time) was determined in 1000 ml of solvent medium at 37°C according to the Rotation-Paddle-Method (USP XX) at 50 rotations per min. For compound A and for nifedipine an aqueous 0.1 HCl solution was used as the solvent medium. After 2 hours the pH was adjusted by addition of a tenside containing buffer solution of pH 6.8. Compound C was tested in a neutral tenside containing aqueous solution.

20 microlitres of a filtered sample of the solution of active agent and of a reference solution were separated chromatographically in 2 columns of a length of 10 cm and a diameter of 4.6 mm, containing substance RP.18; 5 micrometre as a stationary phase and with methanol/water 85:15(v/v) as a mobile phase and at a pressure of 150 bar at room temperature and were measured at a wave length of 326 mm.

The plasma levels of compound B for curves 23 to 26 in fig. 7 and 8 were chromatographically determined as well. A plasma sample of 2 ml, adjusted with NaOH to a pH 13, was extracted with toluene. The toluene was evaporated and the residue dissolved in 25 microlitre of toluene. 2 microlitre of the formed solution were separated at a temperature of 300°C in a OV 17 capillary column (internal diameter of 0.3 mm and a length of 25 m), using helium as a carrier gas; (pressure at the input: 0.7 atm. of excess pressure).

The analysis was carried out at a temperature of 300°C using an electron capture detector and with an argon/methane (90:10 vol/vol) gas mixture (rate 30 ml/min) as additional gas. The retension time of compound B) was 11.5 min.

The calculation of the concentration of compound B was carried out analogously as described for compound A . The detection limit is 50 picogram of active agent per ml of plasma.

Example 1: 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-carboxy-carbonyl-2,6-dimethyl-3-pyridincarboxylic acid ethylester (compound A)

Preparation of the solid dispersion:

4 parts by weight of scaly polyethylene glycol 6000 are melted at 55 to 63°C and heated to about 85°C while stirring.

One part by weight of compound A are added and dissolved completely while stirring at a constant temperature. The solution is then rapidly cooled by pouring it into a metal sheet, where it solidifies in a layer thickness of about 2 mm. After cooling to room temperature the solidified layer is detached from the sheet, reduced to coarse pieces and then passed in stages through sieves of decreasing mesh (2.5, 1.0 and 0.5 mm) or reduced to small pieces in a hammer-mill so that a granulate is produced, usable for the preparation of a tabletting or capsulating mixture.

Example 2:

Hart gelatine capsule

Components:		quantities in mg
1. Compound A - polyethylene glycol 6000 granulate (20%), prepared according to example 1		250.0
2. Placebo granulate of		
Lactose	83 parts	
Cornstarch	10 parts	
Polyvinylpyrrolidon	6 parts	41.0
3. Crosslinked polyvinylpyrrolidone		6.0
4. Silicon dioxide		1.5
5. Magnesium stearate		1.5
		300.0

Both granulates 1. and 2. are mixed. Components 3. to 5. are mixed as well, after which the mixture of 1. and 2. is mixed with the mixture of 3. to 5. and is filled in gelatine capsules of a suitable capacity.

Example 3:

The hard gelatine capsule of example 2 is enteric coated in conventional manner in Wurster column with a mixture of

hydroxypropylmethylcellulosephthalate	33.3 mg
and	
diethylphthalate	3.3 mg

Example 4:

Tablet

Components:	quantity in mg
1. Compound A - polyethylene glycol 6000 granulate (20%), prepared according to example 1	250.0
2. Lactose, anhydrous	188.5
3. Silicon dioxide	2.5
4. Magnesium stearate	9.0
	450.0

The components 1. to 4. are briefly mixed, the mixture is sieved (630 mikrometre mesh), mixed again and tabletted in conventional manner.

Example 5:

Tablet

Components:	quantities in mg
1. Compound A - polyethylene glycol 6000 - granulate (20%), prepared according to example 1	250.00
2. Lactose, anhydrous	177.25
3. Crosslinked polyvinylpyrrolidone	11.25
4. Silicon dioxide	2.50
5. Magnesium stearate	9.00

The components 1. to 5. are mixed and tabletted as described in example 4.

The tablet is enteric coated as described in example 3 with a mixture of

hydroxypropylmethylcellulosephthalate	9 %	
and		
diethylphthalate	9 %	50.00
		500.00

Example 6:

In an analogous manner as described in example 1, a 40% dispersion of compound A in polyethylene glycol 6000 is prepared at a temperature of 125°C. The dispersion granulate is, in a manner as described in example 5, compressed to tablets containing 50 and 100 mg of active agent.

Tablets

Components:	quantities in mg	
1. Compound A - polyethylene glycol 6000 granulate (40%)	125.0	250.0
2. Lactose, anhydrous	65.0	130.0
3. Cross-linked polyvinylpyrrolidone	5.0	10.0
4. Silicon dioxide	1.0	2.0
5. Magnesium stearate	4.0	8.0
enteric coating *	20.0	40.0
	220.0	440.0

* A coating of	percents by weight
hydroxypropylmethylcellulosephthalate	93
Titanium dioxide	3.5
Iron oxide, yellow	3.5

The coating is applied to in conventional manner in a Wurster column

Comparative test No. 1

A conventional uncoated hard gelatine capsule containing a granulate of components 1. to 5. and an external phase of a mixture of components 6. to 9.

	quantities in mg
1. Compound A	50.0
2. Lactose	216.0
3. Cross-linked polyvinylpyrrolidone	6.0
4. Polyoxyethylene-polyoxypropylene polymer	10.0
5. Polyvinylpyrrolidone	7.5
6. Cross-linked polyvinylpyrrolidone	5.5
7. Polyethylene glycol 6000 (solubilizing agent)	10.0
8. Corn starch	52.0
9. Magnesium stearate	3.0
	360.0

was compared with the enteric coated retarded capsule of example 3 and with the uncoated retarded capsule of example 2.

In 8 healthy fasted male volunteers of 19 to 40 years the enteric coated retarded capsules of example 3 produced almost constant plasma levels of compound A (about 5 nanogram/ml) from 3 hours till 28 hours after administration (mean curve 1 in fig. 1).

Conventional hard gelatin capsules caused in the same volunteers the conventional picture of mean curve 2 in fig. 1, the active agent for the most part being released within 6 hours. The areas under both curves 1 and 2 are almost the same: AUC_0^{∞} * = 210 and 196.2 nanograms/ml/h respectively. This indicates that the capsule of the invention has no significant loss of bioavailability.

In a second test the uncoated retarded capsule of example 2 was administered to 8 healthy male volunteers. 4 of the volunteers were also participants in the first test with the enteric coated retarded capsule. In comparison to the conventional capsule (curve 2) a retard effect is obtained (mean curve 3, in fig. 1). However, the uncoated retarded capsule of example 2 has a tendency to cause a drug burst (curve 3).

From both tests it can now be established, that the combination of the new solid dispersion granulate with the enteric coating has an excellent controlled release effect.

The retarded capsules of examples 2 and 3, particularly the enteric coated of example 3, make a once-a-day-administration possible; of the conventional form 2 to 3 capsules have to be taken a day in regular periods of time.

* = AUC_0^{∞} = Area under the curve (extrapolated to infinite)

Comparative test No. 2

The conventional uncoated hard gelatine capsule of comparative test No. 1 was compared again, but instead with the enteric coated retarded tablet of example 5, and tested in another group of 8 healthy male volunteers.

The enteric coated retarded tablet of example 5 produced plasma levels of the mean curve 4 in fig. 2 and the conventional capsule of comparative test No. 1 produced a mean result, comparable with curve 2. The enteric coated retarded tablet of example 5 produced practically constant plasma levels of compound A (about 6 to 7 ng/ml), from 5 and till 32 hours after administration (curve 4).

Again, there is no significant loss in (relative) bioavailability, using the enteric coated retarded tablet . It makes a once-a-day-administration possible. The conventional hard gelatine capsule has to be taken 2 to 3 times a day.

Comparative test No. 3

In a further human study with 8 healthy male subjects, the normal uncoated capsule, described in comparative test No. 1, was compared in a cross-over design with three additional formulations, including the enteric coated retarded tablet of example 6 containing 50 mg of compound A in a 40% solid dispersion in polyethylene glycol 6000.

In this study all formulations were administered to the fasted subjects with 150 ml of water. A standard breakfast was given 2,5 h later.

The mean curve 5 in fig. 3 shows the plasma levels of the enteric coated retarded tablet up to 72 hours.

Concentrations between 3 and 5 ng/ml are obtained from 7 to 36 hours after digestion, a duration of absorption lasting 29 hours. In comparison to the normal capsule the relative bioavailability of the retard tablet was 88%, with a standard deviation of 36%. This value is not statistically different from 100%, on the basis of a paired t-test, indicating no loss of bioavailability.

A remarkable feature of the pharmacokinetic behaviour of this retard tablet is the relatively low intra individual variability, seen in the individual kinetic profiles curves 6 to 13 in fig. 4.

In all cases the plasma levels are seen to fall within the 2 to 8 ng/ml range with no significant drug burst occuring in any subject. Furthermore, the presence of the gastro-ristant coating gave a highly reproduceable lag time prior to absorption (2.6 ± 0.8 h) when the tablets were administered in the fasting state.

These results demonstrate, that an enteric coated tablet composed of a 40% solid dispersion perform an excellent form to permit a once-a-day application of 50 mg and potentially higher doses, e.g. 100 mg of drug.

Example 7: 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid isopropylester (compound B)

Preparation of the solid dispersion and of the dispersion granulate:

6 parts by weight of polyethylene glycol 6000 are mixed with 2 parts by weight of a commercial mixture comprising mono-, di- and triesters of palmitic and stearic acid and glycerol (Precirol*) and with 2 parts by weight of compound B, then melted at a temperature of 75 to 85°C and dissolved as much as possible while intensive stirring at a constant temperature of 70°C. The mixture is then cooled rapidly to room temperature by pouring it onto a precooled metal sheet and kept at 4°C for 3 hours. It solidifies as a layer of approximately 4 mm thickness.

The solidified layer is reduced to coarse particles, which are passed through a hammer mill (type Fitzpatrick, USA) thus producing a granulate usable for the preparation of a tabletting or capsulating mixture.

The characteristic grain size of the RRS-B-distribution = X'= ca 320 micrometre.

n = ca. 3 (reciprocal measure for the distribution range) (H. Sucker, c.s. Pharmazeutische Technologie, Georg Thieme Verlag, Stuttgart 1978, page 110).

Example 8

Tablet

Components:	quantities in mg:
1. Compound B - polyethylene glycol 6000 - fatty acid glyceryl ester mixture-granulate (produced according to example 7)	50.0
2. Lactose, anhydrous	68.8
3. Magnesium stearate	1.2
	120.0

*Trademark of Gattefosse

The components 1. and 2. are briefly mixed (5 min.). The mixture is sieved (mesh: 800 micrometres), sieved again (10 min.), mixed with component 3. (5 min.) and tabletted in conventional manner on a rotary tabletting machine.

The tablets have a diameter of 7 min. and show a compression strength of 46 Newton.

Example 9:

Tablet

Components:	quantities in mg:
1. Compound B - polyethylene glycol 6000-fatty acid glyceryl ester mixture - granulate (according to example 7)	50.00
2. Lactose, anhydrous	61.42
3. Silicon dioxide	0.23
4. Sodium carboxymethylcellulose	2.20
5. Magnesium stearate	1.15
	115.00

The components 1. 2. and 4. are briefly mixed (5 min.), the mixture sieved (mesh: 800 micrometres) and mixed again (10 min.).

The components 3. and 5. are mixed together with a part of the mixture of 1., 2. and 4., sieved (800 micrometres) and mixed with the remainder of the mixture of 1., 2. and 4. (5 min.).

Comparative test No. 4

A conventional uncoated hard gelatine capsule containing a mixture of components 1 to 6

	quantities in mg
1. Compound B	10.0
2. Lactose (filler)	167.0
3. Sodium laurylsulphate (solubilizing agent)	5.5
4. Silicon dioxide (glidant)	1.5
5. Corn starch (desintegrant)	128.0
6. Polyethylene glycol 6000 (solubilizing agent)	8.0
	320.0

was compared with the retarded tablet of example 8. In 8 fasted healthy male volunteers in an age of 19 to 40 years, the retarded tablet of example 8 showed practically constant plasma levels of drug between 2.3 and 1 ng/ml and, on an average, between 1.5 and 1 ng/ml from 2 to 24 hours after administration (see mean curve 23 in fig. 7). The non-retarded conventional capsule showed in the same volunteers the conventional picture of mean curve 24 and a drug release within 6 hours.

The areas under both curves 23 and 24 are practically the same: By comparison of the AUC^{∞} of curves 23 and 24 a relative bioavailability of even 96.2 % for the retard tablet of example 8 could be established.

The retard tablet of example 8 produced, compared with the conventional uncoated hard gelatine capsule, a hardly detectable drug burst.

Whereas 2 to 3 conventional capsules must be administered a day, divided over regular periods of time, the retarded tablet makes a once-a-day administration possible.

Example 10:

Preparation of the solid dispersion and of the dispersion granulate:

10 parts by weight of compound B are dissolved at a temperature of 125°C in liquified polyethylene glycol 6000.

The mixture is quickly cooled to room temperature by pouring it onto a precooled metal sheet and is kept over night.

The solidified layer is reduced to coarse particles and passed through a hammer mill (typ Fitzpatrick, USA) to obtain a granulate, usable for the preparation of a tabletting or capsulating mixture.

Example 11:

Tablet

Components:	quantities in mg
1. Compound B - polyethylen glycol 6000 - granulate (20%, prepared according to example 10)	50.00
2. Lactose, anhydrous	63.85
3. Magnesium stearate	1.15
	115.00

The tablet is produced in an analogous manner as described in example 8 (the sieve had a mesh of 1250 micrometre).

Tablets: diameter 7 mm
compression strength: 40 Newton

Example 12:

The tablet of example 11 is enteric coated in a conventional manner in a Wurster column with a mixture of

	quantities in mg
hydroxypropylmethylcellulosephthalate	13.8
Iron oxide pigment, red.	0.6
Titanium oxide	0.6
	15.0

Comparative test No. 5

Two conventional not retarded capsules each containing a mixture of components 1 to 6 .

	quantities in mg
1. Compound B	5.0
2. Lactose	172.0
3. Sodium laurylsulphate	5.5
4. Silicon dioxide	1.5
5. Corn starch	128.0
6. Polyethyleneglycol 6000 (solubilizing agent)	8.0
	320.0

were compared with the enteric coated retard tablet of example 12.

The test was carried out as described in comparative test No. 4, with the difference that the number of volunteers was raised to 11.

The conventional not retarded capsules both together showed the conventional picture of the mean curve 25 in fig. 8, the drug was released within 10 hours.

The enteric coated retarded tablet of example 12 produced a mean plasma level between 2.5 and 0.8 ng/ml of compound B (mean curve 26) from 3 to 28 hours after administration and had an undiminished relative bioavailability, is compared with the conventional capsules.

The enteric coated retard tablet of example 12 makes a once-a-day administration possible, whereas the conventional capsule has to be taken regularly 2 to 3 times a day.

Example 13: (-)-(S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-1,2,6-trimethyl-3-pyridine-carboxylic-acid isopropylester (compound C)

In an analogous manner as is described in the examples 1 and 7, a 20, 30, 40 and 50% dispersion of compound C in polyethylene glycol 6000 was prepared.

Of the obtained dispersion granulates which contained 50 mg of compound C, the dissolution rate was determined in an aqueous medium according to the Rotating-Paddle-Method (USP XX).

	Dispersion granulate			
Time in hours	20%	30%	40%	50%
0	0	0	0	0
2	100	86	54	27
3		88	60	33
4		88	63	38
5		89	68	44
6		90	72	48

Nifedipine

Example 14

In an analogous manner as is described in examples 1 and 7 a 20% and a 40% dispersion of Nifedipine in polyethylene glycol 6000 was prepared.

Of the obtained dispersion granulates containing 50 mg Nifedipine the dissolution rates were determined in an aqueous medium according to the Rotating-Paddle-Method (USP XX).

	Dispersion granulate	
Time in hours	20%	40%
0	0	0
2	5	0
3	29	11
4	56	20
5	77	31
6	90	41
7	96	46
8	97	51
12	98	63
16	99	72
20	101	79

CLAIMS:

1. A dispersion containing 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester as active agent in a polyalkylene glycol matrix.

2. A dispersion according to claim 1 in a poly(C_{2-3})alkylene glycol matrix.

3. A dispersion according to claim 2 in a polyethylene glycol.

4. A dispersion according to claim 3 in a polyethylene glycol having a molecular weight from 100 to 20.000.

5. A dispersion according to any one of claims 1 to 4 having above 5 percent by weight of crystalline active agent particles of a diameter of up to 5 micrometres.

6. A dispersion according to claim 5,containing additionally entrapped active agent particles of a diameter of up to 100 micrometres .

7. A dispersion according to any one of claims 1 to 6 containing up to 80 per cent by weight of active agent.

8. A dispersion according to any one of claims 2 to 7 in a granulate form.

9. A dispersion according to claim 8, having a diameter of up to 2000 micrometres per granulate particle.

10. A secondary structure of an active agent, obtained from the solid dispersion according to any one of claims 1 to 9 by selective removal of the matrix material.

* C L M S *

11. A secondary active agent structure, obtainable from the solid dispersion according to any one of claims 1 to 10 after removal of the matrix material with an aqueous medium.

12. A secondary active agent structure according to claim 10 or 11, irregularly penetrated by fissurelike channels and containing small pores having a diameter of below 5 micrometre.

13. A secondary structure of 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester having a surface of 1 to 15 m^2/g thereof, measured according to the BET-method and having a pore volume of 20 to 95%, measured by mercury-porosimetry.

14. A pharmaceutical composition containing a dispersion or a structure according to any one of claims 1 to 13.

15. A pharmaceutical composition according to claim 14 in the form of a tablet.

16. A pharmaceutical composition according to claim 14 in the form of a capsule.

17. A pharmaceutical composition according to any one of claims 14 to 16 in enteric coated form.

18. A pharmaceutical composition according to any one of claims 14 to 16, containing a solid dispersion and a fatty acid glycerol ester therein.

19. A pharmaceutical composition according to any one of claims 14 to 16 for oral administration once-a-day, in unit dosage form containing up to 25 mg of active agent.

* C L M S *

20. A controlled release once-a-day oral pharmaceutical composition containing up to 25 mg of 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester as an active agent,and capable of producing on administration a plasma level of 1 to 2.5 ng of active agent/ml for at least 22 hours.

21. A pharmaceutical composition according to claim 20, comprising 10 mg of 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxy-carbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester as active agent.

22. A pharmaceutical composition according to any preceding claim for use in the treatment of hypertension.

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* C L M S *