Description

The invention relates to liquid formulations of dihydropyridines, in particular drop formulations, a process for their preparation, and their use in combating diseases.

It is known that dihydropyridines have very powerful actions which influence the circulation (compare British Patent 1,173,862). Because they are sensitive to light and sparingly soluble, a number of difficulties arise during galenical formulation of drug specialities, which can be seen from the numerous patents and patent applications for particular formulations of this active compound. Thus, for example, U.S. Patent 3,784,684 relates to particular gelatine biteable capsules containing nifedipine, by means of which the coronary action of nifedipine can advantageously be utilized. British Patent 1,456,618 moreover describes solid medicament formulations which likewise ensures (sic) good availability of nifedipine. Solid medicament forms in which the sparingly soluble characteristics of nifedipine are said to be compensated by using certain solubilizing agents and surface-active substances are also described in DE-OS (German Published Specification) 2,822,882. In European Offenlegungsschrift (European Published Specification) 1,247, the absorbency of nifedipine is also said to be improved by using polyethylene glycol and certain porous carrier substances.

European Application EP-A 4,650 discloses liquid formulations of nimodipine with a low content of active compound. If an attempt is made to increase the content of active compound according to the teaching given therein, recrystallization occurs, which results in a decrease in bioavailability. British Application GB-A 2,084,017 also describes a solvent mixture which is capable of dissolving dihydropyridines. However, the active compound is reprecipitated immediately from these solutions on dilution in aqueous media. Thus, these solutions either cannot be diluted with water or else exhibit

recrystallization, even after direct intake, in the gastrointestinal tract, and are thus no longer available in dissolved form for optimum absorption. The same applies to the publication in Chem. Abstr. 91 (1979) Ref. No. 145969m. Chem. Abstr. 91 (1979) Ref. No. 163057s also describes oily solutions which cannot be diluted in water, and the taste of which is unacceptable to the patient.

All the attempts which have hitherto been made to compensate the poor solubility of nifedipine by certain measures and at the same time to ensure good bioavailability have a number of disadvantages. The use of surface-active substances, solubilizing agents and certain carrier substances which have a particular surface, for example are porous, frequently leads to administration forms in which the products are undesirably large. To facilitate swallowing, such tablets or capsules are frequently converted into specific shapes, such as, for example, ellipsoids or longitudinal shapes, but even this no longer gives satisfactory results for products weighing more than 400 mg. More frequent intake of smaller products is not a satisfactory solution either.

A tablet containing nifedipine which is characterized in that the crystalline active compound has a certain specific surface area is also known (DE-OS (German Published Specification) 3,033,919). Following oral administration of the tablet, the plasma concentration rises and remains at a high value for many hours.

There is still a need to provide a formulation for dihydropyridines which has a very rapid absorption of active compound. When the active compound is administered as a tablet, the plasma concentration rises only slowly, because the compound is sparingly soluble. Accordingly, a more rapid onset of action cannot be achieved.

Administration of the active compound in capsule form, in the core of which the active compound is dissolved, leads to a more rapid build-up of the plasma concentration in comparison with the tablet administration form, but in many cases an even more rapid onset of action is desirable.

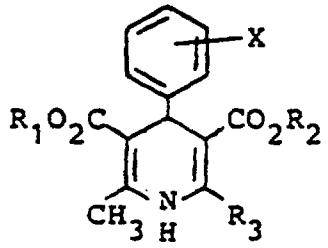
Moreover, there is a need in medicine also to provide drop formulations, since older patients in particular can be motivated more easily to take drops than capsules or tablets.

Furthermore, drop formulations can also be administered to unconscious patients without complications. The active compound can likewise be fed to the body by infusion.

As already described above, all dihydropyridines are sparingly soluble in an aqueous medium. For example, the solubility of nimodipine in water is 0.2 mg per 100 ml.

It has now been found that when certain solubilizing agents are added to the drop solution in a concentration of 20-60 % by weight, based on the total amount of solution, the very sparingly soluble active compound readily dissolves and also remains in solution. It has furthermore been found that when the drop solution according to the invention is diluted with aqueous media, such a dilution remains stable and clear over a relatively long period, depending on the degree of dilution.

The invention thus relates to liquid formulations of dihydropyridines of the formula I



I

in which

R_1 denotes C_1-C_4-alkyl, optionally substituted by C_1-C_3-alkoxy,

R_2 denotes C_1-C_{10}-alkyl, optionally substituted by C_1-C_3-alkoxy, trifluoromethyl or N-methyl-N-benzylamino,

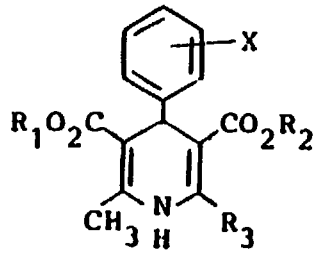
R_3 denotes C_1-C_4-alkyl, cyano or hydroxymethyl and

X denotes 2- or 3-nitro, 2,3-dichloro or a 2,3-ring member consisting of =N-O-N=,

which are characterized in that they consist of dihydropyridines in amounts of 1-5 % by weight, based on 100 parts by weight of a solution consisting of 20 to 60 % by weight, preferably 30-50 % by weight, of a solubilizing agent from the group comprising sorbitan monolaurate, sorbitan monoplamitate, sorbitan monbstearate, sorbitan monooleate, sorbitan sesquiolate, polyethyleneglycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol (20)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristearate, polyethylene glycol (20)-sorbitan monooleate, polyethylene glycol (20)-sorbitan trioleate, glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide, glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide and glycerol polyethylene glycol oxystearate with about 60 moles of ethylene oxide, and 80 to 40 % by weight, preferably 70 to 50 % by weight of a diluent from the group comprising water, ethanol, glycerol 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 600, and, if appropriate, further auxiliaries.

The compounds in the table which follows may be mentioned as preferred dihydropyridines:

Table



No.	X	R^1	R^2	R^3	Generic
1	2-NO_2	CH_3	CH_3	CH_3	Nifedipine
2	3-NO_2	nPrOCH_2CH_2	nPrOCH_2CH_2	CH_3	Niludipine
3	3-NO_2	C_2H_5	CH_3	CH_3	Nitrendipine
4	2-NO_2	CH_3	$(CH_3)_2CHCH_2$	CH_3	Nisoldipine
5	3-NO_2	$CH(CH_3)_2$	$(CH_2)_2$-O-CH_3	CH_3	Nimodipine
6	3-NO_2	C_2H_5	$C_{10}H_{21}$(n)	CH_3	
7	2-Cl	CH_3	CH_2-CF_3	CH_3	
8	2-Cl	C_2H_5	CH_2-CF_3	CH_3	
9	3-NO_2	$CH(CH_3)_2$	n-PrO-CH_2CH_2	CH_3	
10	3-NO_2	CH_3	$C_6H_5CH_2N(CH_3)CH_2CH_2$	CH_3	Nicardipine
11	2,3-Cl_2	C_2H_5	CH_3	CH_3	Felodipine
12	2,3=N-O-N=	C_2H_5	C_2H_5	CH_3	
13	2,3=N-O-N=	CH_3	$CH(CH_3)_2$	CH_3	
14	3-NO_2	C_2H_5	C_2H_5	CH_2OH	
15	3-NO_2	CH_3	CH_3	CN	

n-Pr = n-propyl

Compounds Nos. 1, 3, 4, 5 and 7 may be mentioned as preferred.

Solubilizing agents are understood as being substances which solubilize active compounds which are insufficiently soluble in an aqueous medium, usually with the formation of micelles. Non-ionic surfactants are used for this. The following compounds are suitable solubilizing agents for the drop solutions according to the invention: sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate and sorbitan sesquioleate; polyethylene glycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol (20)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristearate, polyethylene glycol (20)-sorbitan monooleate and polyethylene glycol (20)-sorbitan trioleate, but especially glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide, glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide and glycerol polyethylene glycol oxystearate with about 60 moles of ethylene oxide.

Diluents which can be used in combination with the solubilizing agents are water, ethanol, glycerol, 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 600.

The drops can also be aromatized. Examples of suitable aromas are: peppermint oil, contramarum aroma, cinnamon aroma, boonekamp aroma, orange aroma or lemon aroma.

Sweeteners, such as, for example, saccharin or the sodium salt of saccharin, can also be added.

Since the dihydropyridine derivatives are very sensitive to light, it may prove to be necessary for certain dyestuffs to be added to the drop solutions to protect them from light and for the purpose of stabilization. Suitable dyestuffs can be, for example, apocarotenal, canthaxanthine, tartrazine (E 102), amaranth (E 123) and erythrosine (E 127), but in particular Yellow Orange S (E 110). The concentration of the particular dyestuff is 0.01-0.5 % by weight, preferably 0.1-0.4 % by weight,

based on the liquid formulation.

The liquid formulations can be prepared by warming the solubilizing agent, for example to temperatures of 30 to 70°C, dissolving the dihydropyridine therein, for example with stirring, adding the diluent and, if appropriate, adding the remaining constituents.

Example 1	
Nimodipine	40.000 g
Glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide	400.000 g
Ethanol	500.600 g
Example 2	
Nimodipine	40.000 g
Glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide	400.000 g
Contramarum aroma	0.750 g
Ethanol	500.600 g
Example 3	
Nimodipine	40.000 g
Glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide	435.000 g
Demineralized water	50.000 g
The sodium salt of saccharin	9.000 g
Cinnamon aroma	0.500 g
Ethanol	529.200 g
Example 4	
Nisoldipine	20.000 g
Glycerol polyethylene glycol oxystearate with about 60 moles of ethylene oxide	300.000 g
Demineralized water	100.000 g
Ethanol	533.700 g
Example 5	
Nisoldipine	25.000 g
Polyethylene glycol (20)-sorbitan monolaurate	360.000 g
Saccharin	5.000 g
Ethanol	700.000 g
Example 6	
Nifedipine	40.000 g

Glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide	450.000 g
Polyethylene glycol 400	80.000 g
Demineralized water	80.000 g
Boonekamp aroma	0.800 g
Ethanol	530.600 g
Example 7	
Nifedipine	40.000 g
Glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide	420.000 g
Orange aroma	20.000 g
Saccharin	9.000 g
Ethanol	600.200 g
Example 8	
Nimodipine	20.000 g
Polyethylene glycol (20)-sorbitan monolaurate	380.000 g
Polyethylene glycol 400	80.000 g
Ethanol	607.300 g
Example 9	
3-Methyl 5-trifluoroethyl diester of 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine	30.000 g
Glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide	400.000 g
Lemon aroma	10.000 g
Ethanol	619.600 g
Example 10	
3-mehyl 5-trifluoromethyl diester of 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine	40.000 g
Polyethylene glycol (20)-sorbitan monopalmitate	500.000 g
1,2-Propylene glycol	200.000 g
Peppermint oil	1.000 g
Ethanol	518.000 g
Example 11	
Nifedipine	20.000 g
Glycerol polyethylene glycol oxystearate	

with about 45 moles of ethylene oxide	400.000 g
Orange aroma	20.000 g
Yellow Orange S	4.000 g
Demineralized water	100.000 g
Ethanol	509.700 g

Example 12

Nisoldipine	20.000 g
Glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide	420.000 g
Yellow Orange S	4.000 g
Demineralized water	110.000 g
Ethanol	513.300 g

Because of its properties, the liquid formulation is suitable for the prophylaxis of acute and chronic ischaemic heart disease in the broadest sense, for the therapy of high blood pressure and for the treatment of disorders in cerebral and peripheral blood flow.

In general, it has proved advantageous, in the case of intravenous administration, to administer amounts of about 0.001 to 10 mg/kg of body weight, preferably about 0.05 to 5 mg/kg of body weight, of dihydropyridine per day to achieve effective results, and in the case of oral administration the dosage is about 0.05 to 20 mg/kg of body weight, preferably 0.5 to 5 mg/kg of body weight, per day.

Nevertheless, it may at times be necessary to deviate from the amounts mentioned, as a function of the body weight or the type of administration route, but also because of the animal species and its individual behaviour towards the medicament or the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, whilst in other cases the upper limit mentioned must be exceeded. Where relatively large amounts are administered, it may be advisable to divide these into several individual administrations throughout the day. The same dosage range is envisaged for administration in human medicine. The above statements also apply in the general sense.

Administration of the drop solution gives a more rapid absorption of active compound and surprisingly higher blood level values in comparison with a capsule. Such drop formulations can also be easily administered by stomach tube, without complications, to unconscious patients suffering from a vasospasm following subarachnoidal haemorrhage.

The more rapid absorption of active compound and the higher blood level value may be illustrated by the example of nimodipine with the aid of the following experiments:

6 volunteer test subjects each take 60 mg of nimodipine orally with 200 ml of water. After certain periods of time after taking the active compound, the blood level values are determined by gas liquid chromatography.

After the formulation according to the invention, in accordance with Example 1, has been taken, the highest blood plasma concentration is 115.5 ±78.3 µg/l after 15 minutes. After 24 hours, the corresponding value is below the detection limit of 2 µg/l. The mean area under curve 1 (AUC) is 107.6 ±51.4 h. µg/l. The mean value for the bioavailability is calculated as 8.6 + (sic) 4.6%.

Figure 1 shows the exact course of the curve for the solution (-+-) and, as a comparison, that of the capsule (-O-).

The nimodipine capsule taken for comparison gives, as a value for the highest blood plasma concentration, 60.8 ± 48.0 µg/l after 30 minutes. After 24 hours, the corresponding value is again below the detection limit. The mean value of the bioavailability is calculated as 8.8 ± 4.4 %. The mean area under curve 1 (AUC) is 91.6 ± 35.8 h. µg/l.

The difference in action between the liquid formulation according to the invention and the corresponding capsule can easily be seen from the curve and from the tabular values. After 15 minutes, the blood concentration is 16.6 ± 12.4 µg/l when the capsule is taken, whilst the corresponding value for the liquid formulation is 115.5 ± 78.3 µg/l.

Table 1

Blood concentration in 6 test subjects following oral intake of a liquid formulation containing 60 mg of nimodipine

	time after intake (h)											
	0.25	0.5	0.75	1.0	1.5	2.0	3.0	5.0	8.0	24.0	$AUC_{0-\infty}$ (h.µg/l)	Bioavailability %
1	20	36	22	14	10	7	2	<2	<2	<2	37.6	3.6
2	244	106	57	37	18	12	7	<2	<2	<2	150.1	8.6
3	157	66	43	29	14	11	9	<2	<2	<2	142.0	16.1
4	75	28	20	13	10	7	5	<2	<2	<2	63.2	6.4
5	93	107	59	46	24	19	11	7	<2	<2	162.7	8.5
6	80	55	36	22	17	11	9	3	<2	<2	89.7	-
$\bar{x}$	115.5	66.3	39.5	26.8	15.5	11.2	7.2	2.3	<2	<2	107.6	8.6
±s.d.	78.3	33.9	16.7	13.1	5.4	4.4	3.3	2.4	-	-	51.4	4.6

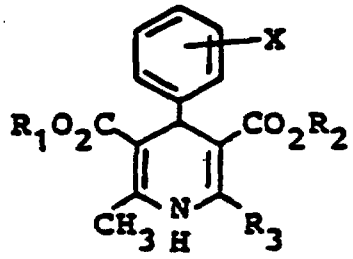
Table 2

Blood concentration in 6 test subjects following oral intake of a capsule containing 60 mg of nimodipine (comparison)

	time after intake (h)												
	0,25	0.5	0.75	1.0	1.5	2,0	3.0	4.0	5.0	8.0	24.0	$AUC_{0-\infty}$ (h.µg/l)	Bioavailability %
	2	27	48	29	27	13	9	5	3	3	2	113.0	7.5
	25	25	83	53	22	14	-	4	<2	<2	<2	89.2	12,7
	35	134	36	19	10	8	3	2	<2	<2	<2	76.5	8.6
	19	41	31	22	19	10	4	2	<2	<2	<2	54.9	5.5
	12	109	78	60	34	24	11	7	6	3	<2	151.8	15.0
	6	29	34	26	19	12	6	9	3	-	<2	64.2	3.3
$\bar{x}$	16.6	60.8	51.5	34.6	21,6	13.3	6.7	4,7	2.5	1.1	<2	91.6	8.8
$\pm$ s.d.	12.4	48.0	23,1	17.4	7.9	5,6	3,5	2.6	2.1	1,3	-	35,8	4.4

Patent Claims

1) Liquid formulations of dihydropyridines of the formula I



I

in which

R_1 denotes C_1-C_4-alkyl, optionally substituted by C_2-C_3-alkoxy,

R_2 denotes C_1-C_{10}-alkyl, optionally substituted by C_1-C_3-alkoxy, trifluoromethyl or N-methyl-N-benzylamino,

R_3 denotes C_1-C_4-alkyl, cyano or hydroxymethyl and

X denotes 2- or 3-nitro, 2,3-dichloro or a 2,3-ring member consisting of =N-O-N=,

characterized in that they consist of dihydropyridines in amounts of 1 to 5 % by weight, based on 100 parts by weight of a solution consisting of 20 to 60 % by weight of a solubilizing agent from the group comprising sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquiolate, polyethyleneglycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol (20)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristerate, polyethylene glycol (20)-sorbitan monooleate, polyethylene glycol (20)-sorbitan trioleate, glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide, glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide and glycerol polyethylene glycol oxystearate with about 60 moles of ethylene oxide, and 80 to 40 % by weight of a diluent from the group comprising water, ethanol, glycerol 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 600, and, if appropriate, further auxiliaries.

* C L M S *

2) Liquid formulations according to Claim 1, characterized in that the proportion of solubilizing agent is 30 to 50 % by weight and that of the diluent is 70 to 50 % by weight.

3) Liquid formulation according to Claim 1, containing a dihydropyridine of the formula I

in which

X represents 2- or 3-nitro or 2-chloro,

R_1 represents methyl, ethyl, propoxyethyl or isopropyl,

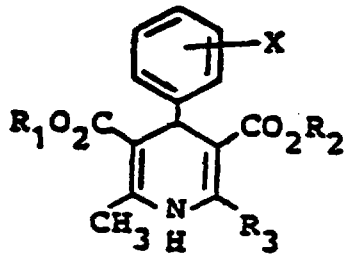
R_2 represents methyl, trifluoromethyl, propoxyethyl, isobutyl or methoxyethyl and

R_3 represents methyl.

4) Liquid formulations according to Claims 1 - 3 for combating diseases.

5) Liquid formulations according to Claims 1 - 3 for combating ischaemic heart disease or high blood pressure and for the treatment of disorders in cerebral and peripheral blood flow.

6) Process for the preparation of liquid formulations of dihydropyridines of the formula I



I

in which

R_1 denotes C_1-C_4-alkyl, optionally substituted by C_2-C_3-alkoxy,

R_2 denotes C_1-C_{10}-alkyl, optionally substituted by C_1-C_3-alkoxy, trifluoromethyl, N-methyl-N-benzylamino,

R_3 denotes C_1-C_4-alkyl, cyano or hydroxymethyl and

X denotes 2- or 3-nitro, 2,3-dichloro or a 2,3-ring member consisting of =N-O-N=,

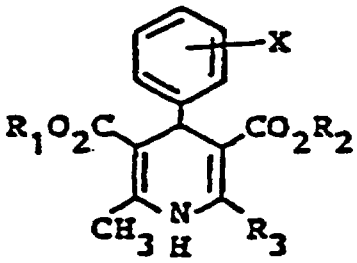
* C L M S *

characterized in that dihydropyridines are dissolved in amounts of 1 to 5 % by weight, based on 100 parts by weight of the finished solution, if appropriate with heating, in 20 to 60 % by weight of a solubilizing agent from the group comprising sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, polyethylene glycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol (2)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristearate, polyethylene glycol (20)-sorbitan monooleate, polyethylene glycol (20)-sorbitan trioleate, glycerol polyethylene glycol oxystearate with about 35 moles of ethylene oxide, glycerol polyethylene glycol oxystearate with about 45 moles of ethylene oxide and glycerol polyethylene glycol oxystearate with about 60 moles of ethylene oxide, 80 to 40 % by weight of a diluent from the group comprising water, ethanol, glycerol 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 600 are then added and, if appropriate, other (sic) auxiliaries are added, the percentages by weight of the solubilizing agent and the diluent being based on the total weight of these two constituents.

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Claims

1. Liquid formulations of dihydropyridines of the formula I



I

in which

R_1 denotes C_1-C_4-alkyl, optionally substituted by C_2-C_3-alkoxy,

R_2 denotes C_1-C_{10}-alkyl, optionally substituted by C_1-C_3-alkoxy, trifluoromethyl or N-methyl-N-benzylamino,

R_3 denotes C_1-C_4-alkyl, cyano or hydroxymethyl and

X denotes 2- or 3-nitro, 2,3-dichloro or a 2,3-ring member consisting of =N-O-N=,

characterised in that they consist of the dihydropyridines in quantities of 1 to 5 per cent by weight, based on 100 parts by weight of a solution consisting of 20 to 60 per cent by weight of a solubilising agent from the group comprising sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquiolate, polyethylene glycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol (20)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristearate, polyethylene glycol (20)-sorbitan monooleate, polyethylene glycol (20)-sorbitan trioleate, glycerol polyethylene glycol oxystearate prepared with about 35 mols of ethylene oxide, glycerol polyethylene glycol oxystearate prepared with about 45 mols of ethylene oxide and glycerol polyethylene glycol oxystearate prepared with about 60 mols of ethylene oxide and 80 to 40 per cent by weight of a diluent from the group comprising water, ethanol, glycerol 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 und polyethylene glycol 600 and optionally other auxiliaries.

2. Liquid formulations according to Claim 1, characterised in that the content of the solubilising agent is 30 to 50 per cent by weight and that of the diluent is 70 to 50 per cent by weight.

3. Liquid formulation according to Claim 1, containing a dihydropyridine of the formula I in which

X represents 2- or 3-nitro or 2-chloro,

R_1 represents methyl, ethyl, propyloxyethyl or isopropyl,

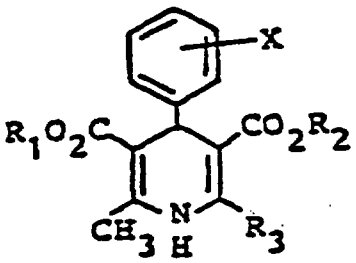
R_2 represents methyl, trifluoromethyl, propyloxyethyl, isobutyl or methoxyethyl and

R_3 represents methyl.

4. Liquid formulations according to Claims 1-3 for combating diseases.

5. Liquid formulations according to Claims 1-3 for combating ischaemic heart disease or high blood pressure and for treating disorders in cerebral and peripheral blood flow.

6. Process for the preparation of liquid formulations of dihydropyridines of the formula I



I

in which

R_1 denotes C_1-C_4-alkyl, optionally substituted by C_2-C_3-alkoxy,

R_2 denotes C_1-C_{10}-alkyl, optionally substituted by C_1-C_3-alkoxy, trifluoromethyl or N-methyl-N-benzylamino,

R_3 denotes C_1-C_4-alkyl, cyano or hydroxymethyl and

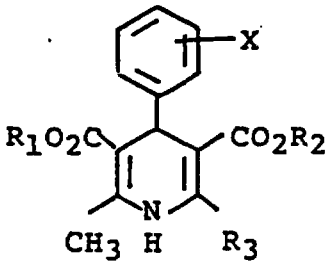
X denotes 2- or 3-nitro, 2,3-dichloro or a 2,3-ring member consisting of =N-O-N=,

characterised in that dihydropyridines are dissolved, in quantities of 1 to 5 per cent by weight, based on 100 parts by weight of the finished solution, optionally with heating, in 20 to 60 per cent by weight of a solubilising agent from the group comprising sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquiolate, polyethylene glycol (20)-sorbitan monolaurate, polyethylene glycol (4)-sorbitan monolaurate, polyethylene glycol

(2)-sorbitan monopalmitate, polyethylene glycol (20)-sorbitan tristearate, polyethylene glycol (20)-sorbitan monooleate, polyethylene glycol (20)-sorbitan trioleate, glycerol polyethylene glycol oxystearate prepared with about 35 mols of ethylene oxide, glycerol polyethylene glycol oxystearate prepared with about 45 mols of ethylene oxide and glycerol polyethylene glycol oxystearate prepared with about 60 mols of ethylene oxide, and then 80 to 40 per cent of a diluent from the group comprising water, ethanol, glycerol 1,2-propylene glycol, polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 600 and added and, if appropriate, the remaining auxiliaries are added, the percentages by weight of the solubilising agent and of the diluent being based on the total weight of these two constituents.

Revendications

1. Préparations liquides de dihydropyridines de formule I:



I

dans laquelle

R^1 est un alcoyle en C_1-C_4, éventuellement substitué par un alcoxy en C_2-C_3,

R^2 un alcoyle en C_1-C_{10}, éventuellement substitué par un alcoxy en C_1-C_3, trifluorométhyle, N-méthyle-N-benzylamino,

R^3 un alcoyle en C_1-C_4, cyano, hydroxyméthyle et

X un 2- ou 3-nitro, 2,3-dichloro, un chaînon nucléaire 2,3 consistant en =N-O-N=,

caractérisées en ce qu'elles consistent en les dihydropyridines en des quantités de 1 à 5% en poids, par rapport à 100 parties en poids d'une solution consistant en 20 à 60% en poids d'un promoteur de dissolution du groupe du monolaurate de sorbitan, monopalmitate de sorbitan, monostéarate de sorbitan, mono-oléate de sorbitan, sesqui-oléate de sorbitan, monolaurate de polyéthylène glycol (20)-sorbitan, monolaurate de polyéthylène glycol (4)-sorbitan, monopalmitate de polyéthylène glycol (20)-sorbitan, tristéarate de polyéthylène glycol (20)-sorbitan, mono-oléate de polyéthylène glycol (20)-sorbitan, trioléate de polyéthylène glycol (20)-sorbitan, oxystéarate de glycérine-polyéthylène glycol à environ 35 moles d'oxyde d'éthylène, oxystéarate de glycérine-polyéthylène glycol à environ 45 moles d'oxyde d'éthylène et oxystéarate de glycérine-polyéthylène glycol à environ 60 moles d'oxyde d'éthylène, et en 80 à 40% en poids d'un diluant du groupe de l'eau, éthanol, glycérine, 1,2-propylène glycol, polyéthylène glycol 200, polyéthylène glycol 400 et polyéthylène glycol 600 et éventuellement en d'autres substances auxiliaires.

2. Préparations liquides selon la revendication 1, caractérisées en ce que la proportion de promoteur de dissolution est de 30 à 50% en poids et celle du diluant de 70 à 50% en poids.

3. Préparation liquide selon la revendication 1 contenant une dihydropyridine de formule I dans laquelle

X est 2- ou 3-nitro ou 2-chloro,

R^1 méthyle, éthyle, propyloxyéthyle, isopropyle

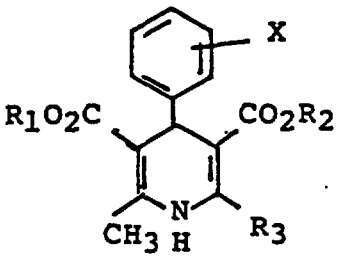
R^2 méthyle, trifluorométhyle, propyloxyéthyle, isobutyle, méthoxyéthyle et

R^3 méthyle.

4. Préparations liquides selon les revendications 1 à 3 pour combattre les maladies.

5. Préparations liquides selon les revendications 1 à 3 pour combattre la maladie cardiaque ischémique, l'hypertension et pour le traitement de dérangements de l'irrigation sanguine cérébrale et périphérique.

6. Procédé de fabrication de préparations liquides de dihydropyridines de formule I:



I

dans laquelle

R^1 représente un alcoyle en C_1-C_4, éventuellement substitué par un alcoxy en C_2-C_3,

R^2 un alcoyle en C_1-C_{10}, éventuellement substitué par un alcoxy en C_1-C_3, trifluorométhyle, N-méthyl-N-benzylamino,

R^3 alcoyle en C_1-C_4, cyano, hydroxyméthyle et

X 2- ou 3-nitro, 2,3-dichloro-, chaînon nucléaire 2,3 consistant en =N-O-N=,

caractérisé en ce qu'on dissout les dihydropyridines en des quantités de 1 à 5% en poids, pour 100 parties en poids de la solution terminée, éventuellement avec chauffage, dans 20 à 60% en poids d'un promoteur de dissolution du groupe du monolaurate de sorbitan, monopalmitate de sorbitan, monostéarate de sorbitan, mono-oléate de sorbitan, sesqui-oléate de sorbitan, monolaurate de polyéthylène glycol (20)-sorbitan, monolaurate de polyéthylène glycol (4)-sorbitan, monopalmitate de polyéthylène glycol (2)-sorbitan, tristéarate de polyéthylène glycol (20)-sorbitan, mono-oléate de polyéthylène glycol (20)-sorbitan, tri-oléate de polyéthylène glycol (20)-sorbitan, oxystéarate de glycérine-polyéthylène glycol à environ 35 moles d'oxyde d'éthylène, oxystéarate de glycérine-polyéthylène glycol à environ 45 moles d'oxyde d'éthylène et oxystéarate de gly-

cérine-polyéthylène glycol à environ 60 moles d'oxyde d'éthylène, puis en ce qu'on ajoute 80 à 40% en poids d'un diluant du groupe de l'eau, éthanol, glycérine, 1,2-propylène glycol, polyéthylène glycol 200, polyéthylène glycol 400 et polyéthylène glycol 600 et on ajoute éventuellement d'autres substances auxiliaires, en l'occurence les pourcentages en poids du promoteur de dissolution et du diluant se rapportant au poids total de ces deux constituants.