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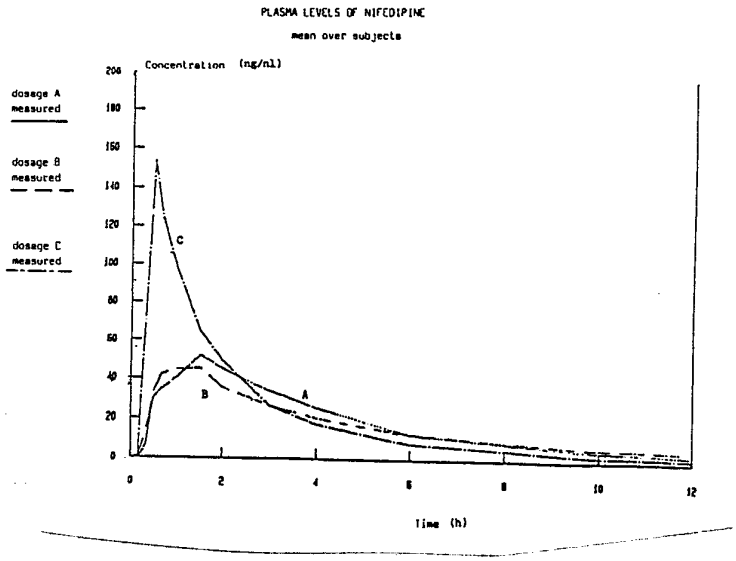

(57) Abstract

Process for preparation of a solid administration form for oral use based on nifedipine with controlled release of the active substance, characterized by the fact that a mixture of nifedipine crystals having a specific surface area between 0.1 and 0.4 m^2/g is prepared, said mixture of crystals is blended with an equal amount by weight of auxiliary vehicle substances, and the resulting mixture so obtained is applied on spheroids of inert substances, by means of suitable binders, in coating pans.

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Controlled release nifedipine preparation.

The present invention relates to a process for preparation of a solid form for oral used based on nifedipine with controlled release of the active substance.

Nifedipine belongs to the group of substances having a calcium antagonistic activity. Its chemical name according to the IUPAC nomenclature is 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridin-carboxylic acid dimethyl ester.

Nifedipine is known to be a substance with high pharmacological activity and its mechanism of action is known and described in the literature. From literature it is also known that nifedipine, administered in such a way as to give rise to plasma levels in the order of 100-200 µg/ml in a short time, is effective to prevent and treat attacks of angina pectoris, while at blood concentrations of 20-80 µg/ml carries out an effective activity in the treatment of arterial hypertension.

Already when taken alone, nifedipine has a low solubility in aqueous solvents and in the range of physiological pH. Use of nifedipine in traditional pharmaceutical forms tends to further increase this feature and in many cases it gives rise to preparations with a very long time of dissolution of the active substance and great variability from one preparation to another.

This causes a variability of absorption of the active substance by the organism, both as values of blood concentration versus time, and total bioavailability, i.e. total amount of nifedipine absorbed in a given time interval.

Improvements in this respect were obtained by using nifedipine substance having a sufficiently high specific surface area of crystals (see German published

patent application DE 3033919 A1), more particularly between 0.5 and 6 m^2/g, or by increasing solubility of nifedipine by forming co-precipitates with auxiliary substances (see European published patent application EP 091247).

These and other systems are clearly effective to obtain pharmaceutical forms based on nifedipine, adapted to give a prompt release and consequent absorption of the active substance and therefore suitable for treating angina pectoris with nifedipine.

The problem of making a pharmaceutical solid form for oral use with a delayed and sustained release of a satisfactory amount of nifedipine remains however unsolved, as the retard administration forms presently available have poor release characteristics in view of the above said poor solubility of the active substance and therefore they show a rather unsatisfactory bioavailability and a considerable lack of time uniformity.

The object of the present invention is therefore the preparation of a pharmaceutical solid form for oral use, adapted to release nifedipine in a time controlled and gradual way, in order to obtain a continuous and prolonged absorption of the active substance by the human being, so as to warrant plasma levels effective for treating arterial hypertension.

For this purpose, nifedipine is used in the form of crystal having a specific surface area between 0.1 and 0.4 m^2/g. The substance is mixed in a suitable equipment with an equal amount by weight of an auxiliary vehicle substance. Among the auxiliary vehicle substances adapted to make pharmaceutical solid forms lactose, corn starch, modified starch are preferred.

Such a mixture is applied on spheroids made of inert substances such as sucrose and starch by using suitable binders, like low molecular weight polyvinylpyrrolidone solutions or polyoxyethyleneglycol solutions, in coating pans.

One of the main problems arising from this type of treatment is connected with the relatively poor distribution of the powder spread on the mass of inert microgranules, which causes an uneven dosage of nifedipine as a direct consequence.

Such an uneven distribution is also reflected, in view of the very low nifedipine solubility, in obtaining batches with very different dissolution speeds and with uneven dissolution speed inside the same batch.

Surprisingly good results were achieved by using particular powder homogenization and deposition techniques so as to obtain a uniform and homogeneous distribution of the active substance powder on the microgranules.

The results of uniformity tests for nifedipine contents on pellets confirmed the above, giving standard deviation values which can be considered similar to the pattern of granulometric distribution of inert microgranules, and therefore to their surface area.

The obtained values of in vitro release of the active substance are moreover reproducible from batch to batch and are homogeneous inside the same batch.

The microgranules so obtain were dosed in hard gelatine capsules in an amount corresponding to 20 mg of nifedipine.

Subsequent tests of bioavailability in human beings showed that the preparations of the present invention allow to obtain plasma levels of nifedipine reaching 20 μg/ml just after 30 minutes and are maintained between 20 and 80μg/ml for 10 hours or more. The bioavailability of these preparations is higher than 90% when compared with a prompt absorption form.

The accompanying drawings show the patterns of the plasma levels of the preparations made according to the present invention, compared with that of a normal administration form (Fig. 1) and that of a retard form presently available on the market (Fig. 2).

As a further confirmation of the favorable characteristics of the preparations made according to the present invention, the following Examples A and B illustrate the production of such a formulation.

EXAMPLE A

2 kg of nifedipine raw material, having a specific surface area between 0.1 and 0.4 m^2/g, are mixed with 2kg of lactose having a granulometry between 10 and 80 μ, using a rotary cylinder mixer. In a coating machine having a stainless steel pan of

600 mm diameter, 8 kg of microgranules consisting of sucrose and corn starch with a granulometry between 0.790 and 0.910 mm are loaded.

The nifedipine powder mixture is loaded in a suitable container provided with feeding suction device, pneumatic vibrator and regulation pressure gauge.

Rotation of the coating pan is started at a speed of 16 rpm and microgranules are wetted with 50 g of a 10% solution of polyvinylpyrrolidone (k 30) in ethyl alcohol. An airless type pump is used to this purpose.

On the rotating wet mass 50 g of nifedipine powder are then sprayed by means of suitable pulverization devices, fed by the above said suitable container. Operations are alternately repeated 80 times in total.

At this point while the coating pan is always rotating, the microgranules are wetted with 200 g of a 12.5% solution of polymethacrylates (Eudragit L) in ethanol: acetone.

On the rotating wet mass 100g of talc are then sprayed by using the same procedure indicated for the nifedipine-lactose mixture. The microgranules so obtained show a good uniformity of nifedipine contents.

Test of in vitro release velocity with the continuous flow method shows a zero order release pattern distinctly modified in comparison with the pure substance and velocity of nifedipine release from microgranules decreases consistently with the increase of the amount of polymethacrylates (Fig. 3).

This relationship is confirmed by the results obtained through a measurement of blood levels of nifedipine in human beings, after administration of several formulations corresponding to the above preparation.

EXAMPLE B

In a coating machine provided with a stainless steel pan of 600 mm diameter, 10 kg of microgranules consisting of sucrose and corn starch with a granulometry between 1.0 and 1.4 mm are loaded.

In two separate suitable containers, 4 kg of nifedipine having a specific surface are between 0.1 and 0.4 m^2/g and 6 kg of corn starch with a granulometry between 20 and 100μ are respectively loaded.

Rotation of the coating pan is started at a speed of 16 rpm and the microgranules are wetted with 100g of a 10% solution of polyoxyethyleneglycol 4000 in ethyl alcohol. An airless type pump is used for this purpose.

Then on the rotating wet mass 200 g of nifedipine and 300 g of corn starch are spayed with two pulverization devices, each connected to one of said containers. These operations are carried out at the same time and the procedure is repeated 20 times.

Test of in vitro release velocity shows a first order release pattern with a total amount of released nifedipine higher than 80% in 8 hours (Fig. 4). Control of uniformity of nifedipine contents confirms the uniform distribution of the active substance on the microgranules.

Indeed, checking the patterns of plasma levels A and B corresponding to the preparations of the above Examples, it is to be noted how they are well differentiated not only in respect of curve C (Fig. 1) of normal nifedipine showing a sharp rise in the first minutes and then likewise rapid decrease, suitable for treating an attack of angina pectoris, but also in respect of curve D (Fig. 2) where it is to be noted that the bioavailability of a retard form prepared with conventional methods is constantly poor, while bioavailability of forms A and B according to the present invention is for superior, especially in the first four hours, and being at the center of the range of therapeutically active plasma levels, it achieves optimal blood levels effective for treating arterial hypertension.

It is therefore clear that the administration forms prepared with the process according to the present invention allow an effective treatment of arterial hypertension, in view of the controlled release of the active substance with reproducible blood levels constantly falling in the range of bioavailability suitable for treating said disorder.

In the light of the results obtained, showing for preparations A and B a clear maintenance for a long time of therapeutically advantageous blood levels, it was considered useful to carry out a further pharmacokinetic study at repeated dosages, thus simulating the posologic scheme suitable for an antihypertensive

treatment for a period of five days.

To this purpose preparation A was chosen and the results of such an experimentation, always carried out in comparison with a conventional retard form already available on the market and with nifedipine in quick release form, fully confirm the results of the preceding tests, again showing for preparation A a better bioavailability in respect of the above mentioned conventional product, without causing however any phenomenon of accumulation with time.

The study was conduced on twelve subjects, of which four female and eight male subjects, whose characteristics are set forth in the following table:

	mean	standard deviation
age (years)	26.5	5.6
height (cm)	171.8	8.8
weight (kg)	67.5	10.3

The following tables 1-3 show the blood levels measured on patients at day 1 of treatment, then during the accumulation phase (day 2,3 and 4) and finally at day 5 in the elimination phase. In the tables, treatment A of days 1-4 and D of day 5 is that effected with one capsule of 20 mg of nifedipine of the present invention, treatment B of days 1-4 and E of day 5 is that effected with two capsules of 10 mg of quick release nifedipine (Adalat), and treatment C of days 1-4 and F of day 5 is that effected with a tablet of 20 mg of delayed nifedipine available on the market (Adalat-Retard). Plasma level concentrations are expressed in ng/ml, while the indicative symbols of the lines of data have the following meanings: mean = mean value; sdev = standard deviation ; sem = standard error of the mean. Times are expressed in minutes, hours and days as indicated.

TABLE 1

PLASMA LEVELS MEASURED AT DAY 1

Time	0h	10 min.	20 min.	30 min.	40 min.	1 h	1h30 min.	2h
Treatment A								
mean	0	0	17.632	34,743	41.684	46.481	46.996	50.936
sdev	0	0	22.039	35,051	36.645	34,354	28.044	27,532
sem	0	0	6.362	10,118	10,579	9,917	8.096	7,948
Treatment B								
mean	0	1,391	124,013	164,99	150.719	110.47	79,74	56,942
sdev	0	4.818	103,359	47.881	31.938	21.044	22,999	15,439
sem	0	1,391	29,837	13,822	9,22	6,075	6,639	4,457
Treatment C								
mean	0	0	11,339	25,163	27,733	31,453	32,133	28.124
sdev	0	0	8.677	13.505	13,931	15,677	18,085	14.792
sem	0	0	2.505	3.898	4,022	4.526	5,221	4.27

TABLE 1 CONTINUED

PLASMA LEVELS MEASURED AT DAY 1

tempo	3h	4h	6h	8h	10h	12h	24h
Treatment A							
mean	52,758	37,31	22,014	14,137	8,548	5,493	0,636
sdev	18,616	13,794	10,658	6,272	5,616	3,796	1,591
sem	5,374	3,982	3,214	1,81	1,621	1,096	0,459
Treatment B							
mean	40,68	26,884	14,635	8,947	5,772	2,931	0
sdev	14,939	9,017	5,782	3,39	2,791	2,468	0
sem	4,312	2,603	1,669	1,022	0,806	0,713	0
Treatment C							
mean	27,749	23,623	16,93	13,998	10,207	8,247	1,557
sdev	10,614	8	7,379	6,542	4,514	4,198	1,673
sem	3,064	2,309	2,13	1,888	1,361	1,212	0,483

TABLE 2

PLASMA LEVELS DURING THE ACCUMULATION PHASE

Time (days)	2	3	4
Treatment A			
mean	10,427	10,125	10,175
sdev	5,399	6,847	4,473
sem	1,559	1,976	1,291
Treatment B			
mean	5,308	3,745	6,693
sdev	3,902	1,979	6,346
sem	1,126	0,571	1,832
Treatment C			
mean	10,073	10,97	11,383
sdev	2,926	5,759	5,445
sem	0,845	1,736	1,572

TABLE 3

PLASMA LEVELS MEASURED AT DAY 5

Time	0h	10 min.	20 min.	30 min.	40 min.	1h	1h30 min.	2h
Treatment D								
mean	10.177	9.581	18.157	37.318	39.087	53.109	62.313	61.113
sdev	4.477	4.439	11.595	25.319	26.853	27.402	27.078	19.159
sem	1.292	1.338	3.496	7.309	8.097	7.91	7.817	5.531
Treatment E								
mean	6.694	12.15	190.655	182.275	151.818	108.3	81.522	61.133
sdev	6.344	10.394	91.761	77.762	62.372	34.238	27.334	15.75
sem	1.831	3.001	26.489	22.448	18.806	9.884	7.891	4.547
Treatment F								
mean	11.387	10.644	17.538	30.727	34.421	38.155	36.5	36.593
sdev	5.449	4.873	8.53	16.059	14.969	12.153	12.433	13.387
sem	1.573	1.407	2.462	4.636	4.321	3.508	3.589	3.864

TABLE 3 CONTINUED

PLASMA LEVELS MEASURED AT DAY 5

Time	3h	4h	6h	8h	10h	12h	24h	48h
Treatment D								
mean	51,102	35,56	20,341	13,446	9.091	6,131	0,222	0
sdev	14,661	9,665	5,389	4,361	4,647	3.512	0,768	0
sem	4,232	2,79	1,556	1,259	1,401	1,059	0,222	0
Treatment E								
mean	37,703	26,418	15,106	9,054	5,481	3,537	0	0
sdev	10.34	6.18	4.918	4,103	3,27	2,347	0	0
sem	2,985	1,784	1,42	1,184	0,944	0,677	0	0
Treatment F								
mean	31,025	26,748	18,899	15,39	11,816	9,781	2,58	0
sdev	10,911	9,328	8,556	7,177	5,059	3,502	1,682	0
sem	3,15	2,693	2,47	2,072	1,46	1,011	0,486	0

On the basis of the data measured and shown in the preceding tables 1-3, mean curves of plasma levels of nifedipine at day 1 (Fig. 5) and at day 5 (Fig. 6) were plotted and it is possible to note even visually that there are no phenomena of accumulation with time of the pharmaceutical preparation according to the present invention.

The following tables 4 and 5 show the pharmacokinetic parameters calculated from the plasma levels of nifedipine measured after treatment, wherein treatments A, B, C, D, E, F have the same meanings as previously indicated, and the symbols of the various parameters are corresponding to the following definitions:

AUC - 1 : trapezium rule, O-last sampling (SD), dosage interval (MD)

AUC - 3 : model curve, O-infinity (SD), dosage interval (MD)

C max : peak concentration

C max(m) : measured peak concentration

T max : peak time

T max(m) : observed peak time

lag-time : start time of absorption

ke : elimination rate constant

tl/2 : elimination half-life

mrt : mean residence time

tl/2 alpha : alpha half-life

tl/2 beta : beta half-life

In the table 4 the pharmacokinetic parameters calculated at day 1 are shown, while in table 5 the same parameters at day 5 are shown.

It may be noted also from these further tables that the pharmaceutical preparation according to the present invention has superior characteristics in comparison with the nifedipine formulations presently available on the market.

TABLE 4

PHARMACOKINETIC PARAMETERS AT DAY 1

Parameter	AUC - 1	AUC - 3	C_{max}	C_{max} (m)	T_{max}	T_{max} (m)
Treatment A						
mean	317.814	337.75	81.1821	75.2575	1.95621	1.91667
sdev	107.601	117.849	29.5296	22.1234	1.07462	1.04083
sem	31.0616	34.0201	8.52447	6.38649	0.310215	0.300463
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h
Treatment B						
mean	356.735	376.218	201.258	177.598	0.475803	0.5
sdev	85.656	90.6711	60.6552	53.4101	0.124258	0.142134
sem	24.7268	26.1745	17.5096	15.4182	0.03587	0.041031
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h
Treatment C						
mean	256.17	304.479	40.3367	40.2008	1.6083	1.54167
sdev	96.3563	98.8216	17.4381	16.2849	1.26191	1.13735
sem	27.8157	28.5273	5.03394	4.70104	0.364281	0.328324
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h

TABLE 4 CONTINUED

PHARMACOKINETIC PARAMETERS AT DAY 1

Parameter	lag-time	ke	t1/2	mrt	t1/2 alfa	t1/2 beta
Treatment A						
mean	0,525066	1.04252	1,6814	5,30887	0,301548	3.51796
sdev	0,569852	1.42199	1.16067	2.13099	0,325898	1,92126
sem	0,164502	0.410493	0.335058	0,615163	0,123178	0,726168
unit	h	1/h	h	h	h	h
Treatment B						
mean	0,137192	0,968181	0,960704	3,13586	0,339462	2,55556
sdev	0,141495	0,767975	0,413819	0,89595	0,254272	0,946419
sem	0,040846	0,221695	0,119459	0,258639	0,073402	0,273208
unit	h	1/h	h	h	h	h
Treatment C						
mean	0,222035	0,574286	3,25592	10,3735	0,656811	9,37473
sdev	0,124974	0,68202	2,18483	4,56167	0,96815	4,60459
sem	0,036077	0,196882	0,630707	1,31684	0,365926	1,74037
unit	h	1/h	h	h	h	h

TABLE 5

PHARMACOKINETIC PARAMETERS AT DAY 5

Parameter	AUC - 1	AUC - 3	C_{max}	C_{max} (m)	T_{max}	T_{max} (m)
Treatment D						
mean	314.36	316.778	77.762	72.1625	1.96585	1.86111
sdev	68.5091	70.5779	26.6592	23.067	1.07274	0.815981
sem	19.7769	20.3741	7.69586	6.65886	0.309672	0.235553
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h
Treatment E						
mean	375.149	365.366	235.435	214.783	0.474823	0.527778
sdev	104.109	104.008	92.2885	79.9681	0.449741	0.475848
sem	30.0537	30.0245	26.6414	23.0848	0.129829	0.137365
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h
Treatment F						
mean	254.105	253.341	45.0807	44.6075	1.29576	1.36111
sdev	77.0613	73.2874	13.9579	13.7587	0.974988	0.984305
sem	22.2457	21.1563	4.02931	3.97181	0.281455	0.284144
unit	hxng/ml	hxng/ml	ng/ml	ng/ml	h	h

TABLE 5 CONTINUED

PHARMACOKINETIC PARAMETERS AT DAY 5

Parameter	lag-time	ke	t1/2	t1/2 alfa	t1/2 beta
Treatment D					
mean	0,243357	1,91282	1,65762	0,201651	4,44231
sdev	0,198066	3,81631	1,05178	0,26219	1,34566
sem	0,057177	1,10167	0,303624	0,117255	0,601799
unit	h	1/h	h	h	h
Treatment E					
mean	0,182272	0,778169	1,06888	0,492011	2,20574
sdev	0,049525	0,358517	0,516385	0,638146	0,78898
sem	0,014297	0,103495	0,149068	0,184217	0,227759
unit	h	1/h	h	h	h
Treatment F					
mean	0,052389	0,180707	12,5622	0,892342	145,944
sdev	0,083218	0,133566	26,9013	0,60656	305,943
sem	0,024023	0,038557	7,76572	0,271262	136,822
unit	h	1/h	h	h	h

It is also to be understood that the administration forms according to the present invention may be subject to all those further processing and treating operations known to a man skilled in the art, and several variations, modifications, additions and/or substitutions may be resorted to the process without departing however from its spirit and scope, as it is also defined in the appended claims.

CLAIMS

1) Process for preparation of a solid administration form for oral use based on nifedipine with controlled release of the active substance, characterized by the fact that a mixture of nifedipine crystals having a specific surface area between 0.1 and 0.4 m^2/g is prepared, said mixture of crystals is blended with an equal amount by weight of auxiliary vehicle substances, and the resulting mixture so obtained is applied on spheroids of inert substances, by means of suitable binders, in coating pans.

2) Process according to Claim 1, characterized by the fact that the auxiliary vehicle substances are chosen from the group comprising lactose, corn starch and modified starch.

3) Process according to Claim 1, characterized by the fact that the inert substances for the spheroids are chosen from the group comprising sucrose and starch.

4) Process according to Claim 1, characterized by the fact that the binders are chosen from the group comprising solutions of low molecular weight polyvinylpyrrolidone and solutions of polyoxyethyleneglycol.

5) Process according to Claim 1, characterized by the fact that the coating pan is being rotated at a speed between 10 and 20 rpm and preferably at 16 rpm.

6) Solid administration form for oral use based on nifedipine with controlled release of the active substance, whenever obtained by the process according to one or more of Claims 1-5.

7) Solid administration form for oral use based on nifedipine in the form of crystals having a specific surface area between 0.1 and 0.4 m^2/g with controlled release of the active substance for treating arterial hypertension, mixed with auxiliary vehicle substances and applied on spheroids of inert substances with a granulometry between 0.4 and 2 mm.

8) Solid administration form for oral use based on nifedipine with controlled release of the active substance according to Claim 7, characterized by the fact that the microgranules are dosed in hard gelatine capsules in an amount of 5 to 50 mg of nifedipine.

9) Solid administration form for oral use based on nifedipine with controlled release of the active substance, substantially as hereinbefore described with reference to the given examples.

10) Process for preparation of a solid administration form for oral use based on nifedipine, with controlled release of the active substance, substantially as hereinbefore described for the above indicated objects and therapeutic use.

11) A pharmaceutical composition comprising inert granules having a coating of particulate nifedipine with a surface area between 0.1 and 0.4 m^2/g, and a binding agent.

12) A composition as claimed in Claim 11 wherein the coating contains a particulate excipient.

13) A composition as claimed in claim 11 or 12 wherein the excipient is lactose.

14) A composition as claimed in anyone of claims 11 to 13, wherein the binding agent is low molecular weight polyoxyethylene glycol.

15) A composition as claimed in anyone of claims 11 to 13, wherein the binding agent is low molecular weight polyvinylpyrrolidone.

16) A composition as claimed in anyone of claims 11 to 15 wherein the granule is sucrose and corn starch.

17) A capsule containing a composition as claimed in anyone of claims 11 to 16.

18) A process for preparing a composition as claimed in anyone of claims 11 to 17 which comprises the steps of coating the inert granules with the particulate

nifedipine and the binding agent and optionally filling the composition into a capsule shell.

FIG. 1

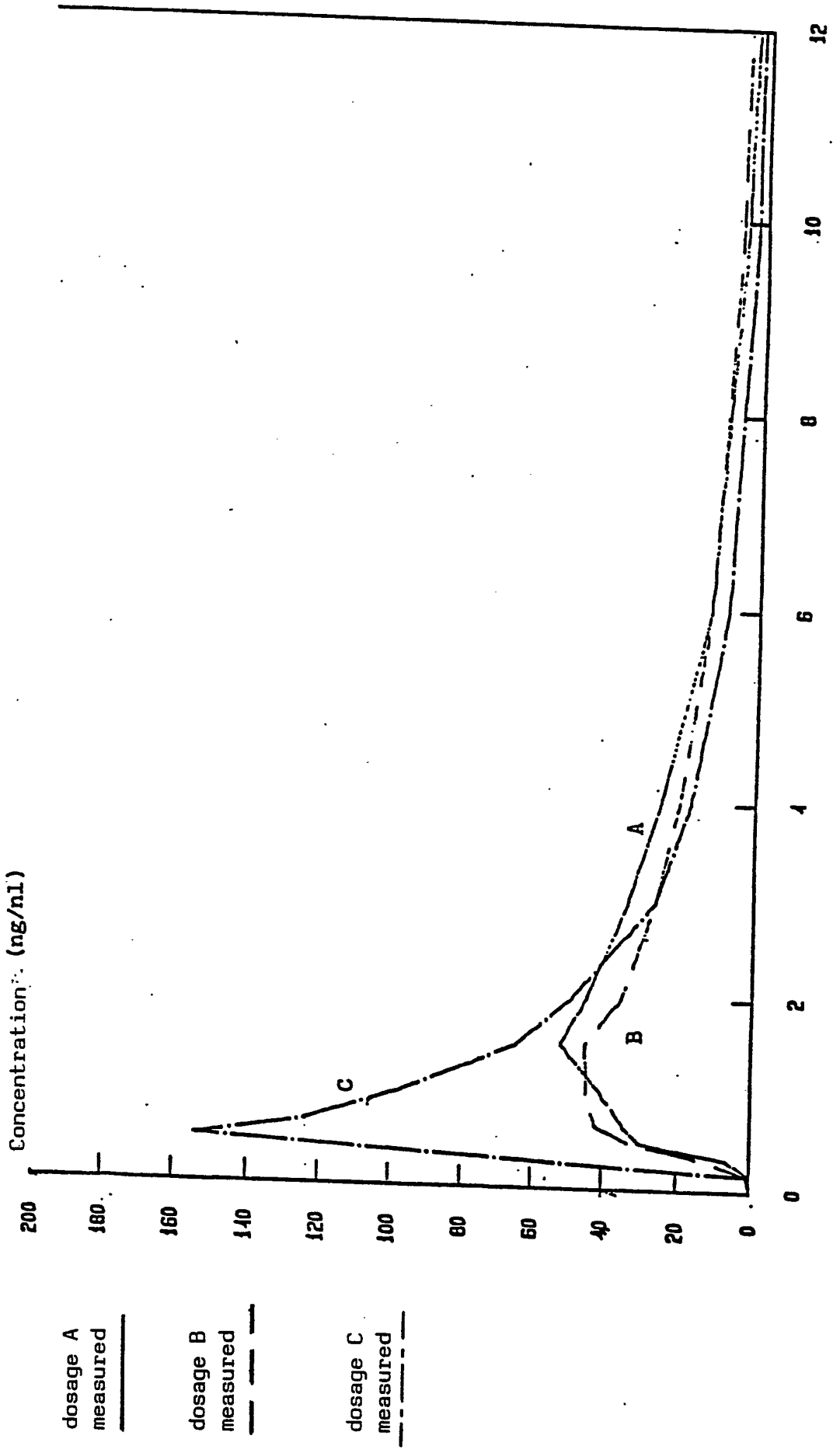

PLASMA LEVELS OF NIFEDIPINE
mean over subjects
Concentration (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (h)
A
B
C
dosage A measured
dosage B measured
dosage C measured

FIG. 2

PLASMA LEVELS OF NIFEDIPINE

mean over subjects

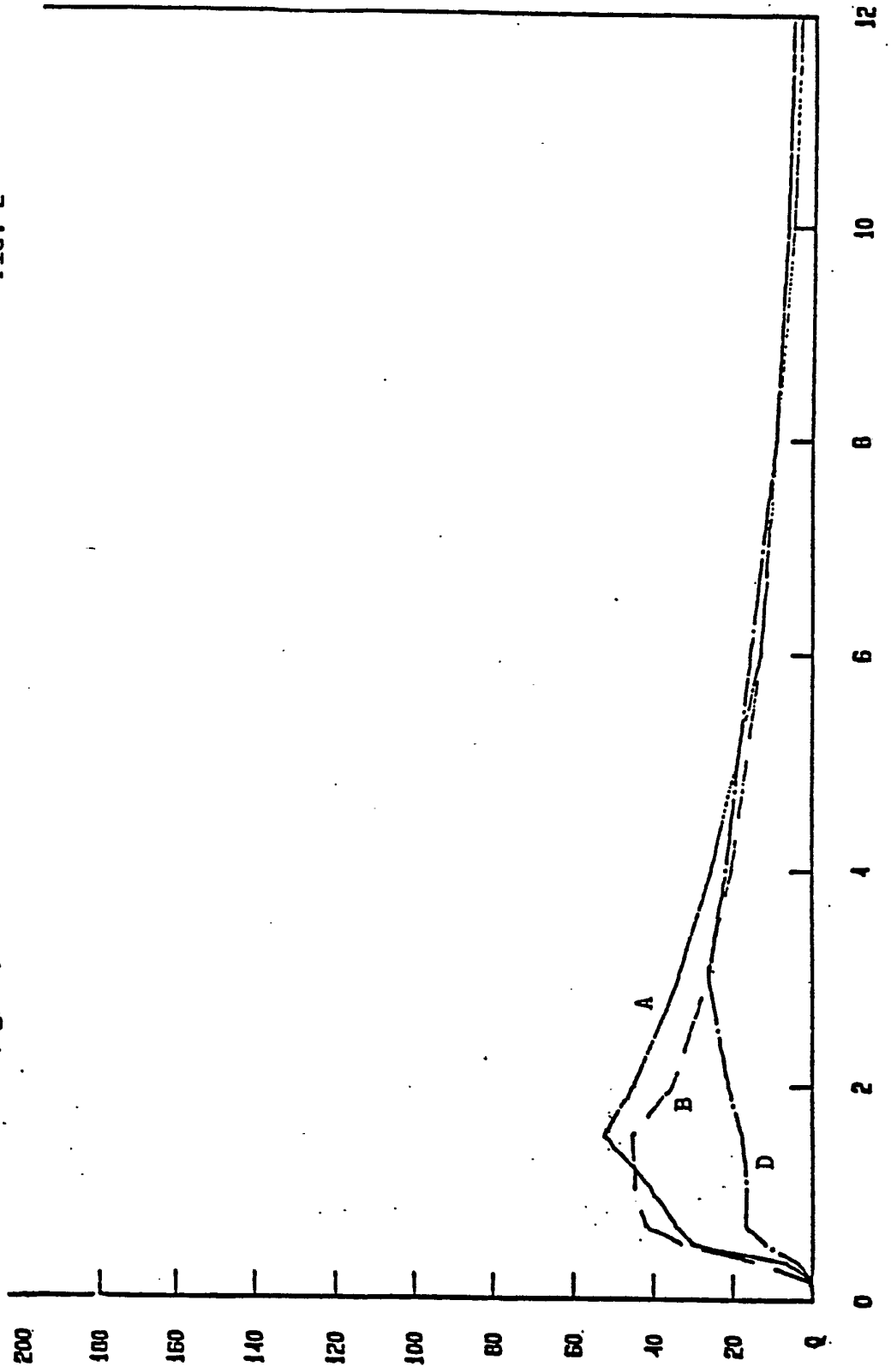


FIG. 3

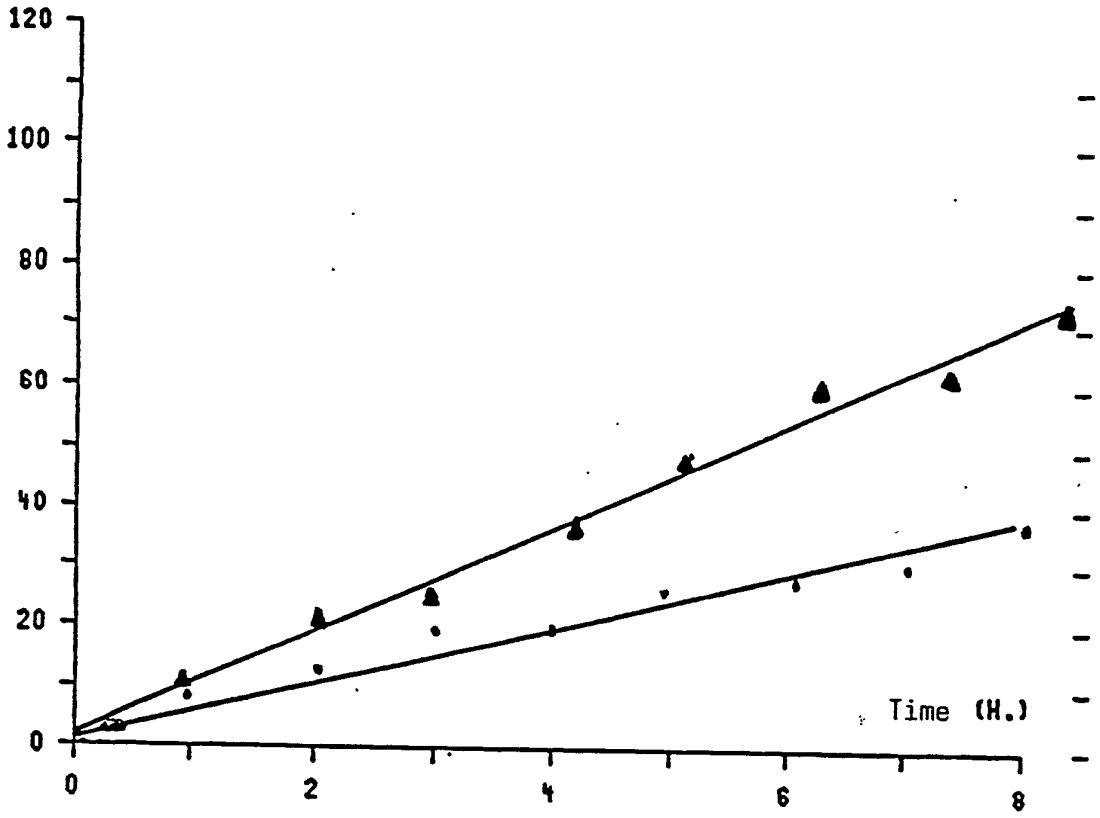
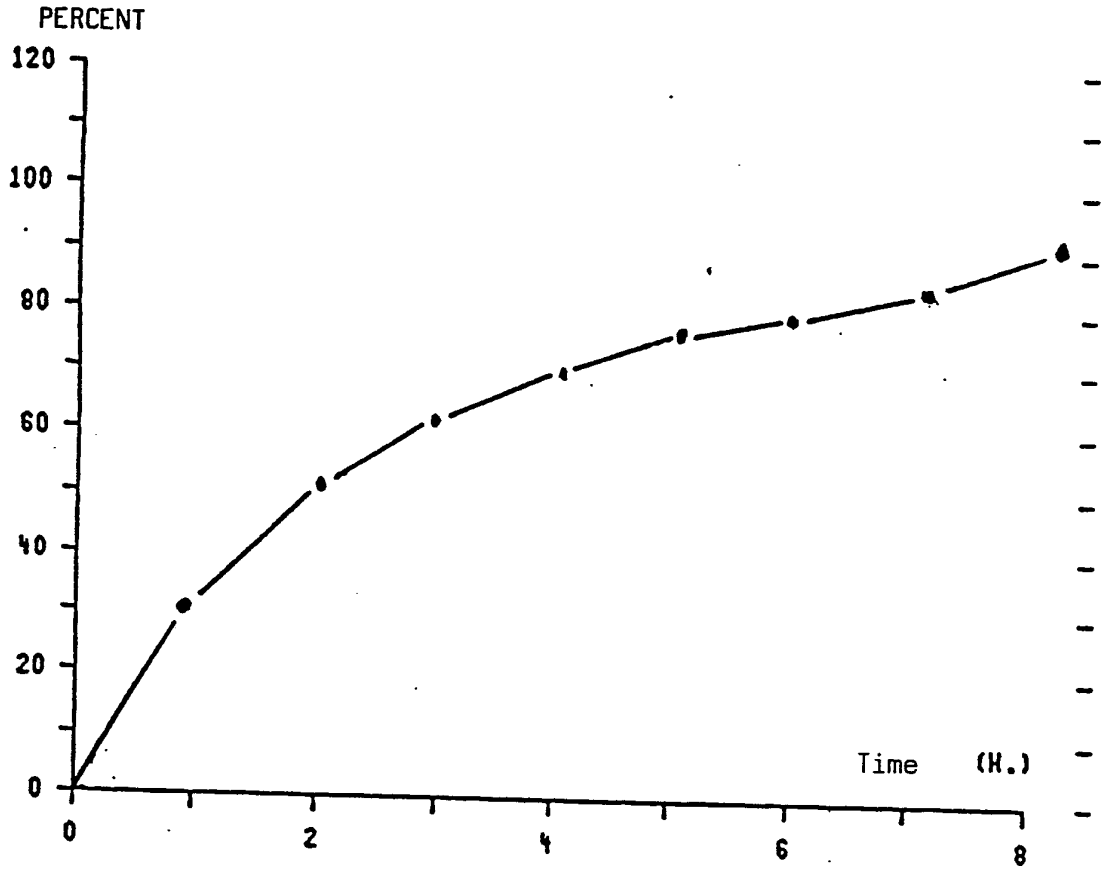

PERCENT
120
100
80
60
40
20
0
0
2
4
6
8
Time (H.)
• NIFEDIPINE EXAMPLE 1 BATCH 199/RR.015
▲ NIFEDIPINE EXAMPLE 1 BATCH 199/RR.017

FIG. 4

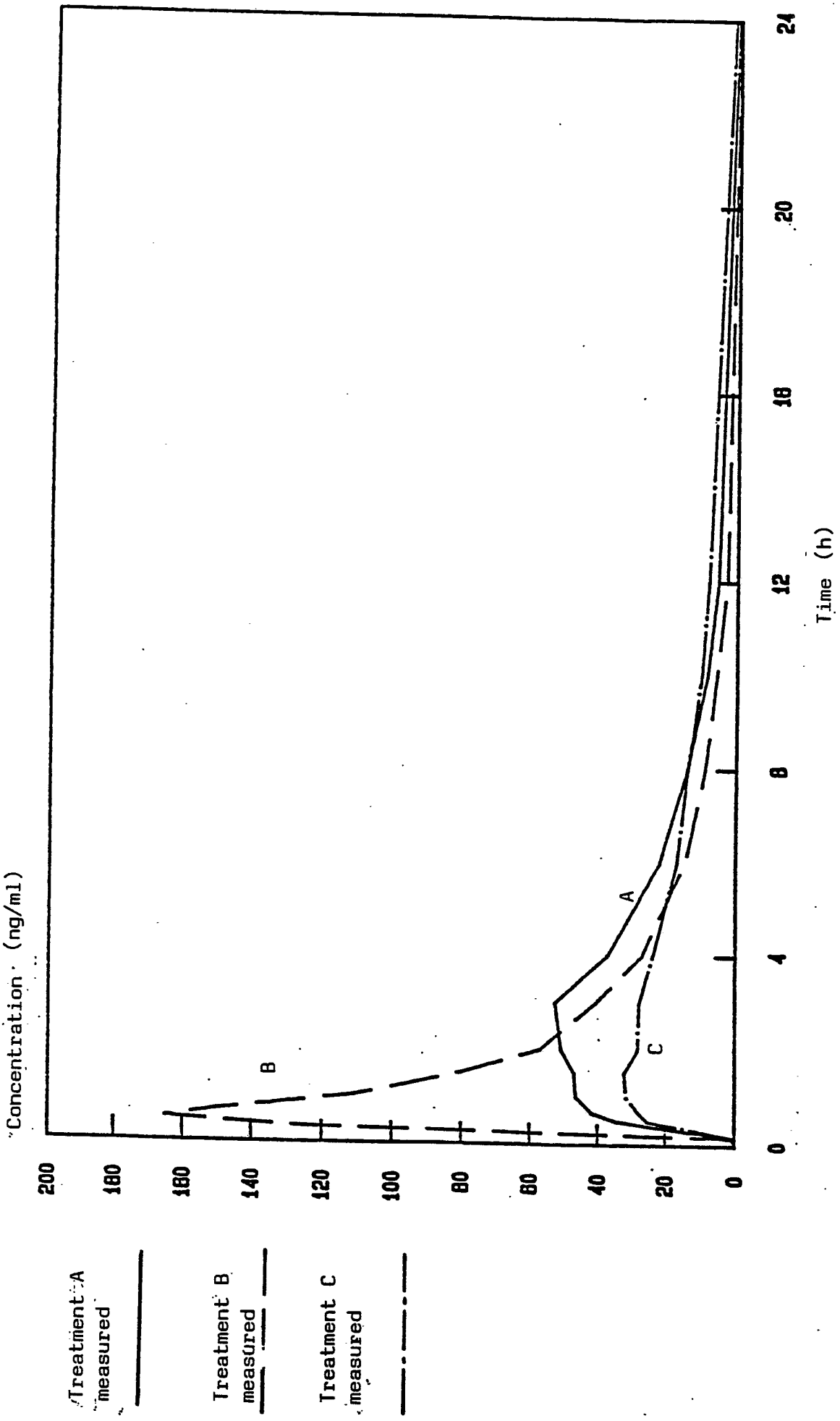


NIFEDIPINE OF EXAMPLE 2 BATCH 199/RR.004

PLASMA LEVELS OF NIFEDIPINE

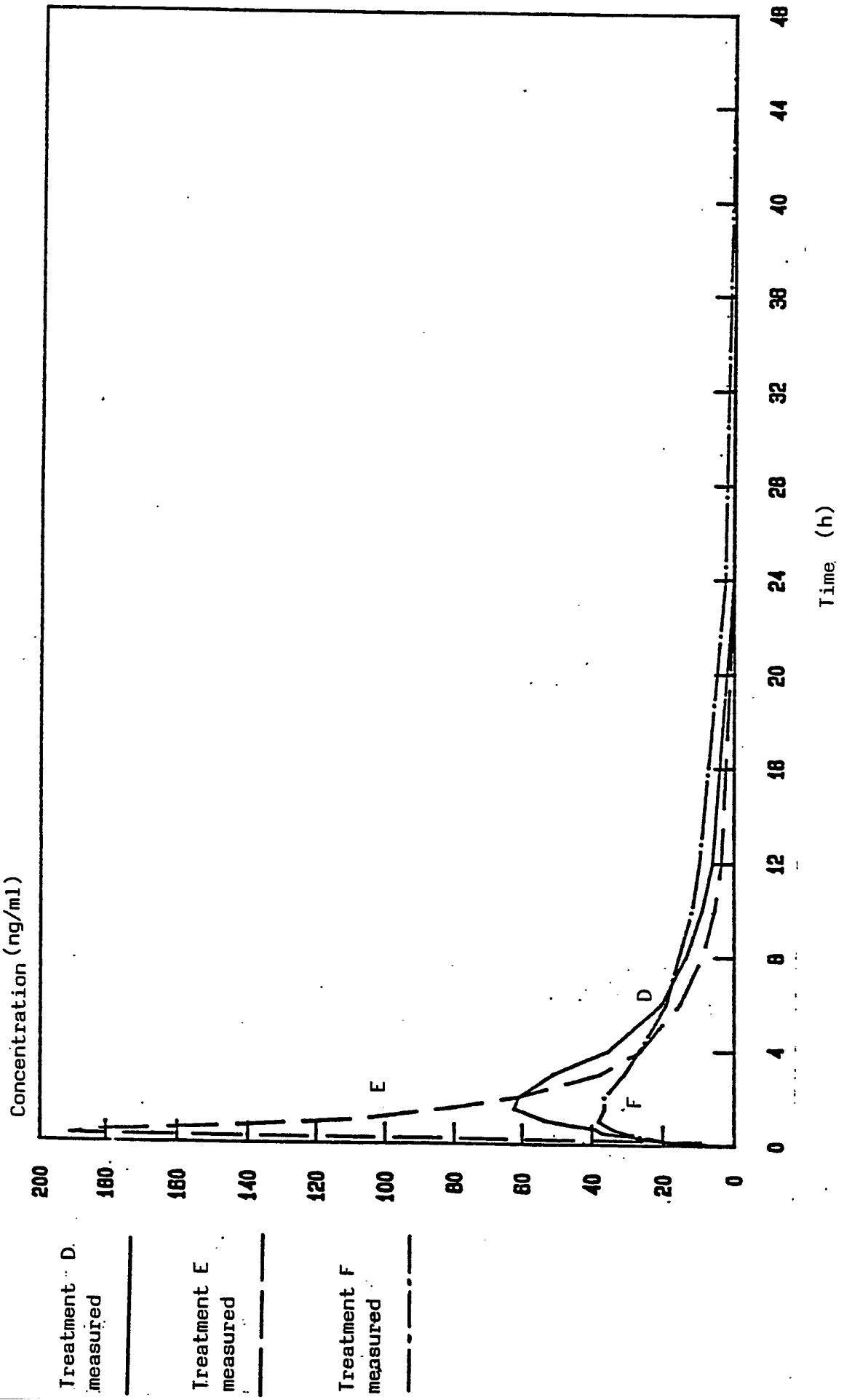
mean over subjects

FIG. 5



PLASMA LEVELS OF NIFEDIPINE

mean over subjects (elimin. phase) FIG. 6



INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 85/00481

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/44; A 61 K 9/52

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A, 0047899 (BAYER) 24 March 1982, see claim 1 & DE, A, 3033919, (cited in the application)	1-18
Y	FR, A, 2453642 (LABAZ) 7 November 1980, see page 13, line 30 - page 14, line 8	1-18
A	Chemical Abstracts, volume 97, nr. 10, 6 September 1982, Columbus, Ohio, (US), page 423, column 2, abstract nr. 78923a & JP, A, 8285316 (KANEBO) 28 May 1982	
A	Chemical Abstracts, volume 98, nr. 16, 18 April 1983, Columbus, Ohio, (US) J. Sugimoto et al.:"Stability and bioavailability of nifedipine in fine granules", page 363, column 2, abstract nr. 132212d & Chem. Pharm. Bull. 1982, 30(12), 4479-88	
A	Chemical Abstracts, volume 99, nr. 6, 8 August 1983, Columbus, Ohio, (US), page 323, column 1, abstract nr 43571y	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17th December 1985	15 JAN. 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	& JP, A, 5877811 (KANEBO) 11 May 1983	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 85/00481 (SA 10805)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/01/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0047899	24/03/82	JP-A-	57050913	25/03/82
		DE-A-	3033919	22/04/82
		AU-A-	7506381	18/03/82
		AT-B-	E5761	15/01/84
		CA-A-	1180277	01/01/85
FR-A- 2453642	07/11/80	None		