CONTROLLED RELEASE NIFEDIPINE PREPARATIONS

This invention relates to controlled release solid pharmaceutical compositions comprising 4-(2'-nitro--phenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydro--pyridine (referred to further on as "nifedipine") as active ingredient.

It is known that nifedipine is a valuable calcium antagonist and is highly useful in the treatment of high blood pressure and coronary diseases (German patent specification No. 1,620,827). The therapeutical use and formulation of nifedipine is however rendered very difficult by the low solubility and high light sensitivity of the active ingredient.

Nifedipine is used in practice in the form of fundamentally two different types of compositions.

One type of nifedipine-containing compositions is used against coronary spasm. In order to achieve the quickest possible relief of the spasm a rapid release of the active ingredient is required which is accompanied by a sudden high blood level.

The other type of nifedipine-containing pharmaceutical compositions is applied for the prevention of coronary spasm

and in the treatment of high blood pressure. In this case sudden high blood level is not required but, quite on the contrary, it would be rather inconvenient because of the increased occurrence of side effects. The therapeutic effect may last from 2-3 hours to 8-10 hours, thus it encompasses compositions of relatively quick effect and those of more or less sustained (prolonged) effect.

According to DOS No. 3,033,919 the low solubility of nifedipine in water and digestive juice is improved by increasing the specific surface area to an extent that the active ingredient is released from the compositions within a therapeutically acceptable period of time. According to the process disclosed in the said patent specification the nifedipine bulk material is ground in a suitable mill, preferably a hammer mill, to a powder having a specific surface area of 0.5-6 m^2/g and finishing the powder thus obtained in the form of solid pharmaceutical compositions by using suitable known carriers and auxiliary agents. Due to the character of the milling procedure the particle size of the active ingredient can be adjusted only within certain limits, and the particle size distribution of the active ingredient may vary to a significant extent even in case of a narrow particle size interval. Thus a particle size interval of about 1-10 μ, which corresponds to a specific surface of 0.5-6 m^2/g, may cause even a 2-3-fold deviation in the maximum of the density function of the particle size and this may exert an influence

on the active ingredient release.

According to Hungarian patent specification No. 193,287 nifedipine-containing two-phase solid pharmaceutical compositions are prepared by dissolving nifedipine and a co-precipitant (preferably polyvinyl pyrrolidone) in an organic solvent, removing the solvent and admixing the co-precipitate thus obtained with 1-5 parts by weight, related to 1 part by weight of the nifedipine content thereof, of crystalline nifedipine having a specific surface of 1.0-6.0 m^2/g and an average particle size of about 10-1 /um. The drawback of this process resides in the fact that nifedipine is contained in a non-uniform granule and therefore on admixing the two different granulations segregation may take place during the tabletting and encapsulating procedure.

Calcium antagonists are more and more frequently used. For the above therapeutical purposes compositions having very precisely defined release characteristics are required, namely in the range extending from compositions which provide suddenly a high blood level through relatively quickly acting preparations to sustained release formulations. Taking into consideration the low solubility of nifedipine in water and digestive juice and also the high light sensitivity thereof, the above objects and requirements can not be solved and fulfilled by means of conventional methods.

It is the object of the present invention to elaborate a process for the simple manufacture of pharmaceutical

compositions which meet the requirements of the given concrete therapeutical field.

According to an aspect of the present invention there is provided a process for the preparation of regulated release solid pharmaceutical compositions comprising 4-(2'-nitro-phenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydro-pyridine (referred to further on as "nifedipine") as active ingredient, which comprises forming one or more solutions that together comprise 1 part by weight of nifedipine, 0.1-1.5 parts by weight of one or more hydrophilic agents selected from hydroxypropyl cellulose and/or polyethylene glycol and/or polyoxyethylene stearate and 0.05-1.5 parts by weight of one or more retarding agent(s) selected from polyvinyl butyral and/or methacrylic acid copolymers, and applying the solution(s) thus obtained onto an inert carrier, (when two or more solutions are used, they are applied simultaneously or in succession and the solvents of the solutions may be the same or different), drying and sieving the product thus obtained and subsequently admixing the same with suitable conventional auxiliary agents and either compressing the mixture thus obtained to form tablets in a known manner and optionally coating the tablets or filling the mixture into capsules, wherein

(i) nifedipine is never applied onto the carrier alone but always in a solution that contains one or both of the hydrophilic agent and the retarding agent, and

(ii) if the hydrophilic agent is applied in a solution that does not contain the retarding agent, then the said solution containing the hydrophilic agent is applied last of all the solutions applied.

The term "relatively quick release pharmaceutical composition" used throughout the specification relates to compositions from which 50% of the active ingredient is released within a period not exceeding one hour (as determined by the method disclosed in the USP) and which, in order to reduce the side-effects on administration of one tablet or capsule, provide a maximal plasma-concentration never exceeding even temporarily the value of 80 ng/ml.

The term "sustained release pharmaceutical composi-

tions" relates to compositions from which 50% of the active ingredient is released within a period longer than one hour.

The present invention is based on the recognition that the factors of uncertainty due to the poor solubility of nifedipine and the differences in the particle structure of the crystalline active ingredient used may be overcome by transforming nifedipine into a solution - i.e. a molecular dispersion - and applying the solution onto a solid carrier together with a hydrophilic agent and a retarding agent either simultaneously or partially separately. The velocity and characteristics of the release of nifedipine may be significantly regulated by the ratio and type of the two auxiliary agents (the hydrophilic agent on the one hand and the retarding agent on the other), the ratio of nifedipine to the total amount of the said two auxiliary agents and also by the way in which solution(s) is (are) applied onto the carrier. Thus not only the speed of release but also the characteristics of the release curve may be varied.

One aspect of the process of the present invention resides in the fact that nifedipine is not applied alone (per se) onto the carrier but the solution of nifedipine always contains a hydrophilic and/or retarding agent or at least a part of the total amount of one or both of these agents.

If the hydrophilic agent or a part thereof is applied onto the carrier alone, this must always be the

last step. One has also to proceed this way if the solution of the hydrophilising agent or a part thereof contains at least part of the nifedipine, too.

The release rate of the active ingredient is completely independent of the further processing of the product, compressing to tablets, coating the same or filling into capsules. In the course of the claimed process the grinding and milling of the active ingredient is eliminated, for this reason the particle structure and particle size distribution of the starting bulk material does not play any role and consequently all the statistical fluctuations arising therefrom are overcome. Advantageously, in to the process of the present invention, nifedipine is processed in the form of a single granulation, therefore no segregation takes place and for this reason blood level and activity remain constant within one batch and these deviations are eliminated.

It is an essential characteristic feature of the present invention that the end-product comprises nifedipine is in crystalline, i.e. not in amorphous, form. Due to the presence of the other components dissolved together with nifedipine, however, these are not necessarily well-defined pure nifedipine crystals but are rather present as a coating layer on the carrier. It is, however, not intended to limit the scope of the present invention by theoretical considerations.

According to the process of the present invention the hydrophilic agent is one or more of hydroxypropyl cellulose and/or polyethylene glycol

and/or polyoxyethylene stearate (e.g. Macrogol stearate Ph. Hg. VII); hydroxypropyl cellulose is especially preferred.

The retarding agent is one or more of polyvinyl butyral and/or methacrylic acid copolymers (e.g. various types of Eudragit, which is a trade mark, (advantageously Eudragit RS)). Polyvinyl butyral proved to be particularly advantageous.

According to a particularly preferred form of realization of the process of the present invention hydroxypropyl cellulose is used as hydrophilising agent and polyvinyl butyral is applied as retarding agent.

In order to accomplish the process of the present invention with the promised result it must be taken into consideration that the hydrophilic and retarding agents exert their desired effect to a different extent. Thus a smaller amount of polyvinyl butyral is sufficient to achieve the same desired retarding effect as a larger amount of Eudragit RS. Similarly, the hydrophilic effect of hydroxypropyl cellulose is stronger than that of polyethylene glycol. For this reason the ratio of the hydrophilising and retarding agents may vary between wide ranges depending on the individual components used and the extent of release to be attained.

As a general rule 0.1-1.5 parts by weight of hydrophilic agent(s) and 0.05-1.5 parts by weight of

retarding agent(s) can be used, related to 1 part by weight of nifedipine.

According to an aspect of the process of the present invention relatively quick release pharmaceutical compositions may be prepared by using 0.3-1.5 parts by weight of a hydrophilic agent and 0.05-0.2 part by weight of a retarding agent, related to 1 part by weight of nifedipine.

According to an other aspect of the process of the present invention sustained release pharmaceutical compositions may be prepared by using 0.1-0.3 part by weight of a hydrophilic agent and 0.2-1.5 parts by weight of a retarding agent, related to 1 part by weight of nifedipine.

According to a particularly preferred form of realization of the process of the present invention relative quick release pharmaceutical compositions may be prepared by using 0.4 part by weight of hydroxypropyl cellulose and 0.07 part by weight of polyvinyl butyral , related to 1 part by weight of nifedipine. According to another particularly preferred form of realization of the process of the present invention sustained release pharmaceutical compositions may be prepared by using 0.1-0.2, preferably 0.1, part by weight of hydroxypropyl cellulose and 0.3-0.5, preferably 0.45, part by weight of polyvinyl butyral , related to 1 part by weight of nifedipine.

According to the process of the present invention nifedipine, the hydrophilic agent and the

retarding agent are used in the form of solution(s) formed in a suitable organic solvent, preferably with a lower alkanol (particularly ethanol or isopropanol) or acetone. Ethanol proved to be particularly suitable for this purpose.

According to the process of the present invention nifedipine, the hydrophilic agent and the retarding agent may be separately dissolved in the organic solvent (preferably ethanol). The solutions thus obtained may be admixed partially in optional ratio and may be applied onto the solid carrier in succession. One may, however, also proceed by admixing the solutions of the above three components, namely nifedipine, the hydrophilic agent and the retarding agent, and applying the single solution thus obtained onto the solid carrier. One may further also proceed by dissolving the nifedipine and the hydrophilic agent(s) in ethanol and adding to the solution thus obtained the separately prepared solution of the retarding agent. According to a still further embodiment of the process of the present invention the hydrophilic agent and the retarding agent are dissolved in the organic solvent and the solution thus obtained is added to the nifedipine solution. In certain cases one may proceed preferably by applying first a solution of nifedipine, the complete amount of the retarding agent and optionally a part of the hydrophilising agent onto the carrier and subsequently spraying the solution comprising the remaining - optionally total - amount of the hydrophilic

agent onto the carrier. Nifedipine solution is, however, never applied onto the carrier alone.

The solution(s) thus obtained are applied onto the solid carrier by methods and equipments known per se by means of a known fluidisation method. The solutions may be sprayed onto the fluidised powder-like carrier with the aid of compressed air. Conventional kneading methods can be used as well. In the latter case, the solution can be applied onto the carrier batch-wise with intermittent drying periods. One may preferably use a conventional fluidising granulating method.

As a result of this operation, the carrier being originally present in the form of a fine powder is transformed into a granular product (granules) and this facilitates further processing (tabletting, encapsulation, etc).

As inert carrier any suitable therapeutically acceptable auxiliary agent or mixtures thereof can be used, e.g. microcrystalline cellulose and/or lactose and/or a disintegrating agent (e.g. croscarmellose).

The granules prepared from the solid carrier and the solution(s) applied (sprayed) on the same are dried and sieved by any suitable method known per se whereupon they are admixed with further known auxiliary agents (e.g. talc, magnesium stearate; disintegrating agents, e.g. croscarmellose) and are compressed into tablets (preferably to convex tablets) by known methods or filled into capsules.

Because of the light sensitivity of nifedipine the tablets are preferably coated. The coating may be made of a conventional sugar type or a film. In order to protect the tablets from light it is preferred to use a coating which comprises a suitable dye or pigment. Red and/or orange dyes, red and/or orange aluminium pigments, iron oxide pigments may be used optionally together with titanium dioxide. The wall of the capsule may also advantageously comprise one or more of the above light protecting agent(s).

The advantage of the process of the present invention is that controlled (regulated) release solid nifedipine-containing pharmaceutical compositions can be prepared in a simple way readily feasible on industrial scale, too, by varying the amount and ratio of the hydrophilising agent and the retarding agent.

The process of the present invention is suitable for the preparation of both relatively quick and sustained release pharmaceutical compositions. The release of the active ingredient is independent of the pH of the medium, i.e. from the period of time during which the pharmaceutical composition stays in the stomach. According to the process of the present invention the release of the active ingredient does not depend on the particle structure of the active ingredient,either; the milling and grinding procedures accompanied by various factors of uncertainty are eliminated. Nifedipine is contained in a uniform granulation and for this reason no segregation occurs on tabletting or en-

capsulating.

According to a further aspect of the present invention, there are provided regulated release nifedipine-containing solid pharmaceutical compositions prepared by the process as defined above.

According to a still further aspect of the present invention there are provided regulated release solid pharmaceutical compositions comprising as active ingredient nifedipine, 0.1-1.5 parts by weight of at least one hydrophilic agent selected from hydroxypropyl cellulose and/or polyethylene glycol and/or polyethylene stearate and 0.05-1.5 parts by weight of at least one retarding agent selected from polyvinyl butyral and/or methacrylic acid copolymers, related to 1 part by weight of nifedipine, and optionally suitable inert conventional pharmaceutical auxiliary agents, said nifedipine, hydrophilic agent(s) and retarding agents being coated on an inert carrier.

The relatively quick release solid pharmaceutical compositions of the present invention preferably comprise 0.3-1.5 parts by weight of the hydrophilic agent and 0.05-0.2 parts by weight of the retarding agent, related to 1 part by weight of nifedipine.

The sustained release solid pharmaceutical compositions of the present invention preferably comprise 0.10-0.3 parts by weight of the hydrophilic agent and 0.2-1.5 parts by weight of the retarding agent, related to 1 part of nifedipine.

The hydrophilic agent(s), retarding agent(s) and the ratio thereof and the other components may be those as disclosed above.

Further details of the present invention are to be found in the following Examples without limiting

scope of protection to the Examples.

Example 1

30 g of nifedipine are dissolved in 240 g of ethanol. To the solution thus obtained at first a solution of 6 g of hydroxypropyl cellulose (Klucel LF) in 50 g of ethanol, then 240 g of Eudragit RS (12.5% of Eudragit RS, 35% of acetone, 52.5% of isopropanol: C.A. Reg. No. 33,434-24-1) are added. The solution thus obtained is sprayed on a mixture of 184.5 g of microcrystalline cellulose, 84 g of lactose and 1.5 g of crospovidone (USP XXI/N.F. XVI) by means of a fluidization procedure. The mixture is sieved on a 0.9 mm sieve and then dried. Thereafter 18 g of crospovidone, 9 g of talc and 1.5 g of magnesium stearate are added. The mixture is compressed to tablets and coated or filled to capsules, respectively. According to the method of USP XXI or PhHg VII (rotating basket; 150 r.p.m.; in 900 ml of 0.1 N hydrochloric acid) from the tablets thus obtained 50% of the active ingredient is released within 3 hours (T_{50} = 3 hours).

Example 2

35 g of nifedipine are dissolved in 280 g of ethanol. At first 280 g of an Eudragit RS 12.5% solution are added to the solution whereupon the solution is sprayed onto a mixture of 210 g of cellulose and 70 g of lactose. A solution of 5.25 g of hydroxypropyl cellulose and 100 g of ethanol is sprayed onto the mixture whereupon it is dried and sieved. 21 g of crospovidone, 7 g of talc and 1.75 g of magnesium stearate are added and the mixture is compressed

to tablets. The half-value time amounts to T_{50} = 4 hours.

Example 3

40 g of nifedipine are dissolved in 320 g of ethanol whereupon a solution of 16 g of polyvinyl butyral (Mowital* B) and 270 g of ethanol is added. The solution thus obtained is sprayed onto a mixture of 180.8 g of cellulose and 32 g of lactose. A solution of 6 g of hydroxypropyl cellulose and 115 g of ethanol is then sprayed onto the carrier which is dried and sieved. 40 g of croscarmellose (USP XXI/N.F. XVI: cross-linked sodium carboxymethyl cellulose; disintegrating agent), 4 g of talc and 1.2 g of magnesium stearate are added. The mixture is compressed to tablets as described in Example 1 and coated, if necessary. Half-value time, TD_{50} = 5 hours.

Example 4

50 g of nifedipine are dissolved in 400 g of ethanol and the solution thus formed is admixed with a solution of 25 g of polyvinyl butyral and 300 g of ethanol. The solution thus obtained is sprayed onto a mixture of 232.5 g of cellulose and 50 g of lactose, whereupon a solution of 10 g of hydroxypropyl cellulose and 190 g of ethanol is sprayed onto the carrier. After drying and sieving 25 g of croscarmellose and 7.5 g of talc are added. The mixture is compressed to tablets and coated. The half-value time, TD_{50} amounts 6 hours.

*Trade Mark

Example 5

30 g of nifedipine, 30 g of polyethylene glycol 6000 (Macrogol 6000) and 3 g of polyoxy 40 stearate (Macrogol stearate) are dissolved in 240 g of ethanol and the solution thus formed is admixed with a solution of 21 g of polyvinyl butyral and 200 g of ethanol. The solution thus obtained is sprayed onto a mixture of 195 g of cellulose, 60 g of lactose and 18 g of crospovidone. After drying and sieving 5.9 g of crospovidone, 1.5 g of magnesium stearate and 0.6 g of colloidal silica are added. The mixture thus obtained is compressed to tablets and coated. TD_{50} = 4.5 hours.

Example 6

One proceeds as described in Example 4 except that the ethanolic solution of hydroxypropyl cellulose is divided into two parts, one half is added to the ethanolic solution of nifedipine and polyvinyl butyral before spraying while the second portion is sprayed subsequently onto the carrier.

Example 7

8 kg of nifedipine are dissolved in 64 kg of warm ethanol, whereupon to the solution thus formed a solution of 3.2 kg of hydroxypropyl cellulose, 0.56 kg of polyvinyl butyral and 32 kg of ethanol is added. The solution thus obtained is sprayed in a fluidizing granulating equipment onto a mixture of 36.8 kg of microcrystalline cellulose, 12 kg of lactose and 2.4 kg of croscarmellose. The granules are then passed through a sieve of about 0.7 mm and dried.

8 kg of croscarmellose, 0.8 kg of talc and 0.24 kg of magnesium stearate are added and the mixture is pressed into tablets, which are convex on both sides, weigh 0.09 g and comprise 10 mg of nifedipine, with the aid of tools having a diameter of 7 mm. The tablets are coated with a film of about 4 mg based on hydroxypropyl methyl cellulose; the said layer comprises about 7.5% of yellow iron oxide pigment and about 20% of titanium dioxide.

On determining the in vitro delivery (Ph.Hg. VII "method of rotating paddle", 150 r.p.m., in 900 ml of 0.1 N hydrochloric acid, page 473) it has been found that 50% of the active ingredient is dissolved within 45-60 minutes. According to in vivo test a maximal blood level on dogs is produced after about 60 minutes /W. Vater et al.: Arzneim. Forsch. 22, 1 (1972); H. Suzuki: J. Chromatogr. 341, 341 (1985)7.

Example 8

12.00 kg of nifedipine are dissolved in 96.00 kg of a warm ethanol whereupon the solution thus formed is admixed with a solution of 5.4 kg of polyvinyl butyral and 48.00 kg of ethanol. The solution thus obtained is sprayed onto a mixture of 54.00 kg of microcrystalline cellulose, 18.00 kg of lactose and 3.84 kg of croscarmellose in a Glatt WSG 200 fluidizing granulating equipment. Spraying rate 2.0 kg/minute, the temperature of the fluidizing air amounts to 45 °C. After termination of spraying the granules are passed through an about 0.7 mm sieve on an oscillating granulating machine. The granules are

returned into the container of the fluidizing granulating machine and sprayed with a solution of 1.20 kg of hydroxypropyl cellulose and 24.00 kg of ethanol. The mixture is dried in the same equipment and sieved.

In a suitable homogenizer 12.00 kg of croscarmellose, 1.20 kg of talc and 0.36 kg of magnesium stearate are admixed with the dry granules thus obtained. The mixture is either pressed into tablets weighing 0.18 g with normal concave punches having a diameter of 8 mm or filled into hard gelatine capsules. The tablets are coated with a conventional sugar-based coating. The mixture can also be filled into hard gelatine capsules whereby the wall of the capsule or the coating may preferably comprise light non-transmitting (opaque) materials in the orange region (e.g. titanium dioxide, iron oxide pigment, red or orange aluminium pigment).

According to in vitro test 50% of the active ingredient is dissolved within about 4 hours (USP XXI or Ph.Hg. VII "paddle method", 150 r.p.m).

Example 9

500 g of nifedipine are dissolved in 4000 g of warm ethanol whereupon to the solution thus formed a solution of 50 g of hydroxypropyl cellulose, 175 g of polyvinyl butyral and 2000 g of ethanol is added. The solution thus obtained is sprayed in a fluidizing granulating apparatus onto a mixture of 2250 g of microcrystalline cellulose, 750 g of lactose and 160 g of croscarmellose.

After termination of the spraying procedure the granules are sieved lump-free and fluidizing granulation is continued by spraying a solution of 50 g of hydroxypropyl cellulose and 1000 g of ethanol onto the carrier. The granules are dried and sieved whereupon 500 g of croscarmellose, 50 g of talc and 15 g of magnesium stearate are added. The granules are compressed into lentil-form tablets which are then film-coated by applying a hydroxypropyl methylcellulose solution which comprises light non-transmitting pigments (titanium dioxide, iron oxide pigment, preferably red or orange aluminium pigment).

According to in vitro test 50% of the active ingredient are dissolved within about 2 hours (USP XXI or Ph.Hg. VII "paddle method", 150 r.p.m.).

Example 10

110 g of nifedipine are dissolved in 880 g of ethanol under heating on a water-bath at a temperature of about 50 °C. After complete dissolving a solution of 44 g of polyvinyl butyral and 720 g of ethanol are added. Into a container of a Glatt WSG 1 type fluidizing granulating equipment 498 g of microcrystalline cellulose and 88 g of lactose are introduced, fluidization is started at an inlet air temperature of 40 °C and the previously prepared solution is sprayed onto the carrier at a spraying rate of 40 ml/minute. The pressure of the fluidizing air amounts to 0.5 bar.

During the spraying operation the temperature of

the solution is maintained with the aid of a water-bath of about 50 °C. In the course of this step the spraying rate of the solution is gradually increased to 50 ml/minute. Spraying is carried out for 40 minutes, the temperature of the leaving air amounts to 22-23 °C.

After applying the complete volume of liquid onto the carrier a solution of 16.5 g of hydroxypropyl cellulose and 320 g of ethanol is sprayed in. The granules thus obtained are passed through a 0.9 mm sieve and dried in the fluidizing apparatus; the temperature of the leaving air amounts to about 30 °C. To the dry granules 110 g of croscarmellose, 11 g of talc and 2.75 g of magnesium stearate are added. The homogenized mixture thus obtained is compressed into tablets weighing 0.16 g and comprising 20 mg of nifedipine with the aid of a normal concave punch which has a diameter of 8 mm.

The tablets are film-coated. The coating contains titanium dioxide and reddish brown iron oxide pigment or a mixture of "Sunset yellow" and "Neococcin" aluminium pigments.

According to the test methods described in USP XXI or Ph.Hg. VII (in 0.1 N hydrochloric acid, "basket-method") the tablets show the following active ingredient release:

Time (hour)	Released nifedipine, %
1	20
3	40
5	53

Example 11

50 g of nifedipine and 75 g of polyethylene glycol 6000 (Macrogol 6000) are dissolved in 300 g of ethanol. To the solution thus formed a 12.5% solution of 200 g of Eudragit RS (see Example 1) is added. Into the container of a Uniglatt type fluidizing granulating apparatus a mixture of 150 g of lactose and 150 g of microcrystalline cellulose is introduced and the above solution is sprayed onto the carrier. The temperature of the spraying solution is adjusted to 50 °C and maintained continuously at this value with the aid of a water bath; the temperature of the fluidizing air amounts to 40 °C; spraying rate 12 g/minute. After termination of the spraying step the granules are dried in the same equipment and thereafter passed through a 0.9 mm sieve. After addition of 50 g of crospovidone (see Example 1) the mixture is homogenized and then filled into light non-transmitting (opaque) orange, red or brown hard gelatine capsules, size 2. The capsule fill weighs 0.2 g.

According to the method disclosed in USP XXI or Ph. Hg. VII the capsules show the following active ingredient release:

Time (hours)	Released nifedipine, %
1	22
2	32
3	41

continued

Time (hours)	Dissolved nifedipine, %
4	48
5	54
6	60

CLAIMS

1. A process for the preparation of regulated release solid pharmaceutical compositions comprising 4-(2'-nitro-phenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydro-pyridine (referred to further on as "nifedipine") as active ingredient, which comprises forming one or more solutions that together comprise 1 part by weight of nifedipine, 0.1-1.5 parts by weight of one or more hydrophilic agents selected from hydroxypropyl cellulose and/or polyethylene glycol and/or polyoxyethylene stearate and 0.05-1.5 parts by weight of one or more retarding agent(s) selected from polyvinyl butyral and/or methacrylic acid copolymers, and applying the solution(s) thus obtained onto an inert carrier, (when two or more solutions are used, they are applied simultaneously or in succession and the solvents of the solutions may be the same or different), drying and sieving the product thus obtained and subsequently admixing the same with suitable conventional auxiliary agents and either compressing the mixture thus obtained to form tablets in a known manner and optionally coating the tablets or filling the mixture into capsules, wherein

(i) nifedipine is never applied onto the carrier alone but always in a solution that contains one or both of the hydrophilic agent and the retarding agent, and

(ii) if the hydrophilic agent is applied in a solution that does not contain the retarding agent, then the said solution containing the hydrophilic agent is applied last of all the solutions applied.

2. A process according to claim 1, which comprises using 0.3-1.5 parts by weight of a hydrophilic agent and 0.05-0.2 parts by weight of a retarding agent, related to 1 part by weight of nifedipine.

3. A process according to claim 1, which comprises using 0.10 - 0.3 parts by weight of a hydrophilic agent and 0.2-1.5 parts by weight of a retarding agent, related to 1 part by weight of nifedipine.

4. A process according to any of claims 1 to 3, which comprises using hydroxypropyl cellulose as hydrophilic agent and polyvinyl butyral as retarding agent.

5. A process according to any one of claims 1, 2 or 4, which comprises using 0.4 part by weight of hydroxypropyl cellulose as hydrophilic agent and 0.07 part by weight of polyvinyl butyral as retarding agent, related to 1 part by weight of nifedipine.

6. A process according to any one of claims 1, 3 or 4, which comprises using 0.1-0.2 part by weight of hydroxypropyl cellulose as hydrophilic agent and 0.3-0.5 part by weight of polyvinyl butyral as retarding agent, related to 1 part by weight of nifedipine.

7. A process as claimed in claim 6, wherein 0.1 parts by weight of hydroxypropyl cellulose and/or 0.45 parts by weight of polyvinyl butyral are used, based on 1 part by weight of nifedipine.

8. A process according to any of claims 1-7, which comprises using a solution of nifedipine, a hydrophilic agent and a retarding agent formed with a lower alkanol or acetone.

9. A process according to claim 8, wherein the alkanol comprises ethanol or isopropanol.

10. A process according to claim 8 or claim 9, which comprises using a solution of nifedipine, hydroxypropyl cellulose and polyvinyl butyral formed with ethanol.

11. A process according to any of claims 4 to 10, which comprises spraying a solution of nifedipine, hydroxypropyl cellulose and polyvinyl butyral in ethanol onto a solid carrier.

12. A process according to any of claims 4 to 10, which comprises admixing the ethanolic solutions of nifedipine, hydroxypropyl cellulose and polyvinyl butyral completely or partly and applying the solution(s) onto a solid carrier.

13. A process according to any of claims 1 to 12, wherein the solid carrier comprises optionally micro-crystalline cellulose and/or lactose and/or croscarmellose.

14. A process according to any of claims 1 to 13, which comprises using as further auxiliary agent(s) in the preparation of tablets or capsules talc, magnesium stearate, silicium dioxide and a disintegrating agent.

15. A process as claimed in claim 14, wherein the auxiliary agent comprises croscarmellose or crospovidone.

16. Regulated release solid pharmaceutical compositions, comprising as active ingredient crystalline nifedipine whenever prepared by the process according to any of claims 1 to 15.

17. Regulated release solid pharmaceutical compositions, comprising as active ingredient nifedipine, 0.1-1.5 parts by weight of at least one hydrophilic agent selected from hydroxypropyl cellulose and/or polyethylene glycol and/or polyethylene stearate and 0.05-1.5 parts by weight of at least one retarding agent selected from polyvinyl butyral and/or methacrylic acid copolymers, related to 1 part by weight of nifedipine, and optionally suitable inert conventional pharmaceutical auxiliary agents, said nifedipine, hydrophilic agent(s) and retarding agents being coated on an inert carrier.

18. Solid pharmaceutical compositions according to claim 17, comprising 0.3-1.5 parts by weight of one or more of the said hydrophilic agents and 0.05-0.2 part by weight of one or more of the said retarding agents, related to 1 part by weight of nifedipine.

19. Solid pharmaceutical compositions according to claim 17, comprising 0.10-0.3 part by weight of one or more of the said hydrophilic agents and 0.2-1.5 parts by weight of one or more of the said retarding agents, related to 1 mole of nifedipine.

20. Solid pharmaceutical compositions according to any one of claims 17 to 19, comprising hydroxypropyl cellulose as the hydrophilic agent and polyvinyl butyral as the retarding agent.

21. Solid pharmaceutical compositions according to claim 18 or 20, comprising, as hydrophilic agent, 0.4 part by weight of hydroxypropyl cellulose and, as retarding agent, 0.07 part by weight of polyvinyl butyral, related to 1 part by weight of nifedipine.

22. Solid pharmaceutical composition according to claim 19 or 20, comprising 0.1 part by weight, of hydroxypropyl cellulose as the hydrophilic agent and 0.3-0.5 part by weight of polyvinyl butyral as the retarding agent, related to 1 part by weight of nifedipine.

23. Solid pharmaceutical composition according to claim 22, which comprises 0.1 parts by weight of hydroxypropyl cellulose and/or 0.45 parts by weight of polyvinyl butyral, related to one part by weight of nifedipine.

24. Solid pharmaceutical compositions according to any of claims 17 to 23, comprising as solid carrier optionally microcrystalline cellulose and/or lactose and/or croscarmellose.

25. Solid pharmaceutical compositions according to any of claims 17 to 24, comprising as further auxiliary agent talc, magnesium stearate, silicium dioxide and a disintegrating agent.

26. Solid pharmaceutical composition as claimed in claim 25, wherein the auxiliary agent comprises croscarmellose or crospovidone.

27. A process of preparing a regulated release pharmaceutical composition substantially as herein described in any one of Examples 1 to 11.

28. A regulated release pharmaceutical composition substantially as herein described in any one of Examples 1 to 11.