SUSTAINED-RELEASE MICROGRANULES CONTAINING DILTIAZEM AS ACTIVE PRINCIPLE

The present invention relates to novel forms of sustained-release (SR) microgranules containing Diltiazem as active principle.

Diltiazem is a calcium-antagonist benzothiazepine derivative which is useful for the treatment of arterial hypertension. It may be administered in various forms: tablets, injectable solutions or gelatin capsules containing sustained-release granules. The latter have the advantage of allowing the administration to be taken as a single dose required for daily treatment.

Various forms of Diltiazem SR microgranules have been described in the prior art, the most advantageous being that described in patent application EP-A-0,149,920, comprising a core combining Diltiazem with a water-soluble organic acid, in particular fumaric acid. The reason for this is that Diltiazem, or its pharmaceutically acceptable salts, are sparingly soluble at neutral or basic pH, and the presence of a water-soluble organic acid has proven to be particularly important, making it possible to create a buffered acidic microenvironment, promoting both the dilution and the absorption of the Diltiazem in areas of the digestive tract where the pH is too high. It has, nevertheless, been observed that for these SR forms, the solubilization and absorption of Diltiazem were dependent on the absorption of food, and are different when uptake of the microgranules is carried out on an empty stomach or during meals.

Organic-acid-free SR microgranules have been described in patent application EP-A-0,613,370. The core of the microgranules consists here of a neutral grain coated with a succession of layers of a water-soluble polymer, on the one hand, and of Diltiazem on the other hand.

For these various forms, the sustained release of the active principle is ensured by one or more layers coating the core of the microgranules, generally com-

bining two types of film-forming polymer material, one being water-insoluble and the other water-soluble.

The present invention relates to a novel form of SR microgranules containing Diltiazem, or a pharmaceutically acceptable salt thereof, which is free of water-soluble organic acid, making it possible to obtain solubilization and absorption of the active principle which are at least equivalent to those obtained in the presence of an acid. In addition, the present invention relates to a simple novel form of SR microgranules containing Diltiazem, which is easy to prepare.

The microgranules according to the invention comprise a neutral granular support coated with an active layer comprising Diltiazem or a pharmaceutically acceptable salt thereof, a surfactant and a binder, and a layer which ensures sustained release of the active principle (referred to hereinbelow as the SR layer).

More particularly, the microgranules in accordance with the present invention may be of several categories.

The first category is represented by microgranules whose SR layer ensures slow sustained release of the active principle.

The second category is represented by microgranules whose SR layer ensures rapid sustained release of the active principle.

The difference between these two categories of monolayer microgranules lies essentially in the thickness of the coating agent contained in the SR layer. Indeed, the thicker this SR layer is, the slower will be the diffusion of the active principle.

The dissolution profile of each of these two types of microgranule is determined in vitro using water as dissolution medium, and gives the following specifications:

Rapid microgranules:

Hours	Dissolution	Preferred Dissolution
2h	0-45%	≤30%
6h	≥50%	≥65%

Slow microgranules:

Hours	Dissolution	Preferred Dissolution
12h	0-60%	≤30%
20h	≥50%	≥45%

Mixture:

Hours	Dissolution	Preferred Dissolution
1h	≤15%	≤15%
6h	≤55%	25-55%
10h	30-70%	30-60%
16h	30-85%	55-85%
22h	-	≥80%

The present invention also relates to a third category of microgranules resulting from the coating of the SR layer which ensures slow sustained release of the active principle, that is to say of the SR layer of microgranules of the first category above, from another active layer comprising:

- Diltiazem or a pharmaceutically acceptable salt thereof as active principle,
- a surfactant, and
- a binder,

itself coated with an external layer which ensures rapid sustained release of the active principle contained in

this active layer.

In other words, these so-called "bilayer" microgranules consist, from the centre to the periphery, of a neutral granular support, of a first active layer, of an SR layer ensuring slow sustained release of the active principle contained in the first active layer, of a second active layer and of an SR layer ensuring rapid sustained release of the active principle contained in the second active layer.

It is understood that for the so-called "bilayer" microgranules, only the specifications described above and corresponding to the slow and mixed microgranules can be applied.

Advantageously, a so-called protective coating or intercalating layer is applied to the microgranule between the SR layer ensuring slow sustained release of the active principle and the second layer of active principle.

Indeed, it has been shown that during application of the second layer of Diltiazem, and/or during dissolution of the microgranules, interactions are established between the Diltiazem and the SR layer located between the two active layers, thereby leading to the modification of sustained release of the Diltiazem contained in the first active layer. This intercalating layer acts as it were as insulation between the two layers concerned, protecting them from each other. Another means of obtaining the same result would consist in using for the SR layer in question a coating agent which does not interact with the Diltiazem.

The neutral granular support consists of any pharmaceutically acceptable neutral granular support, with an average diameter of between 0.4 and 0.9 mm, preferably 0.4 and 0.6 mm. These are preferably grains consisting of sucrose and starch in a weight ratio in the region of 75/25, such as those described under the name "Sugar Spheres" (Handbook of Pharmaceutical Excipients, 2nd Ed., The Pharmaceutical Press, London, 1994).

The hydrochloride is preferably among the

pharmaceutically acceptable salts of Diltiazem.

The surfactant may be an anionic, nonionic, cationic or amphoteric surfactant. It is preferably an anionic surfactant. Among the anionic surfactants are alkali metal (C_{10}-C_{20})alkyl sulphates, preferably sodium lauryl sulphate, alkali metal (C_{10}-C_{20})alkyl sulphonates or alkali metal (C_{10}-C_{20})alkyl benzenesulphonates. The term alkali metal is preferably understood to refer to sodium or potassium.

The binder consists of any pharmaceutically acceptable binder which is useful for coating neutral granular supports, in particular pharmaceutically acceptable polymers such as the polyvinylpyrrolidones described under the name povidone (Handbook of Pharmaceutical Excipients, 2nd Ed., The Pharmaceutical Press, London, 1994), or hydroxypropyl methyl celluloses (HPMC), polyethylene glycols (PEG), etc.

The active layer comprising the Diltiazem may also comprise other common additives, such as a plasticizer.

In general, the active principle/neutral granular support weight ratio is in the region of 4/1. The term active principle is understood to refer to Diltiazem or the pharmaceutically acceptable salts thereof.

The active principle/surfactant weight ratio is advantageously between 99/1 and 95/5, preferably about 98/2.

The active principle/binder weight ratio is itself between 99/1 and 90/10, preferably in the region of 97/3.

The monolayer microgranules according to the invention preferably comprise the following components for the support and the active layer, the percentages being given on a weight basis for a total of 100:

- neutral granular support	20 - 25%
- active principle	70 - 75%
- surfactant	0.5 - 5%
- binder	0.5 - 10%
- plasticizer	0 - 5%.

The bilayer microgranules according to the invention preferably comprise the following components for the support and the active layers, the percentages being given on a weight basis for a total of 100:

- neutral granular support	10 - 20%
- active principle	75 - 85%
- surfactant	0.5 - 5%
- binder	0.5 - 10%
- plasticizer	0.5 - 5%.

Each SR layer consists of a coating agent which ensures the sustained release, optionally combined with one or more common additives, in particular a bioavailability adjuvant and/or a plasticizer and/or a lubricant.

The coating agent ensuring the sustained release is preferably a water-insoluble film-forming polymer, such as polymethacrylates (Handbook of Pharmaceutical Excipients, 2nd Ed., The Pharmaceutical Press, London 1994), in particular poly(ethyl acrylate, methyl methacrylate, trimethylammoniumethyl methacrylate chloride), which are marketed under the brand name Eudragit® RS.

The bioavailability adjuvant is preferably a fatty acid ester of polyoxyethylene, in particular those described under the name Polysorbate (Handbook of Pharmaceutical Excipients, 2nd Ed., The Pharmaceutical Press, London, 1994), in particular those marketed under the brand name Montanox®.

The lubricant consists of a pharmaceutically acceptable common lubricant used in the preparation of microgranules, in particular talc.

The plasticizer is a pharmaceutically acceptable common plasticizer used for the preparation of microgranules, in particular esters of citric, phthalic and sebacic acids, in particular aliphatic esters such as triethyl citrate, dibutyl sebacate or diethyl phthalate, and mixtures thereof.

Preferably, a phthalic acid ester is used for each active layer and a mixture of esters of citric and sebacic acids is used for each SR layer.

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When it is present, the protective coating or intercalating layer consists of a methacrylic type polymer, a plasticizer, a lubricant and optionally a bioavailability adjuvant.

The monolayer microgranules according to the invention advantageously have the following final composition, the percentages being expressed on a weight basis for a total of 100%:

- neutral granular support	10 - 20%
• active layer:	
- active principle	45 - 65%
- binder	0.5 - 2%
- surfactant	0.5 - 1%
- plasticizer	0.5 - 1%
• SR layer:	
- coating agent	10 - 30%
- bioavailability adjuvant	0.05 - 0.15%
- plasticizer	2 - 10%
- lubricant	2 - 10%.

The bilayer microgranules according to the invention advantageously have the following final composition, the percentages being expressed on a dry weight basis for a total of 100%:

- neutral granular support	10 - 20%
• active layer:	
- active principle	45 - 60%
- binder	0.5 - 2%
- surfactant	0.5 - 1%
- plasticizer	0.5 - 1%
• SR layer:	
- coating agent	10 - 30%
- bioavailability adjuvant	0.05 - 0.15%
- plasticizer	2 - 10%
- lubricant	2 - 10%.

The active principle content of each active layer may be identical or different depending on the rate and the amount of active principle which it is desired to release over time. The necessary adaptations depending on the aim to be achieved are within the capability of any

person skilled in the art.

The microgranules according to the invention are prepared according to the usual techniques for mounting the active principle onto the neutral granular support followed by coating with the SR layer, the operation being repeated for the bilayer microgranules.

The active principle is mounted by discontinuous spraying of an aqueous-alcoholic solution containing the binder, the surfactant and optionally the plasticizer, in alternance with sequences of dusting of the active principle and sequences of leaving to stand.

The Diltiazem microgranules thus obtained are then screened and dried.

Coating with each SR layer is then carried out by spraying an aqueous suspension containing the coating agent and the usual additives. The SR microgranules thus obtained are then screened and dried.

This operation of coating with each SR layer is repeated as many times as required to obtain the desired release kinetics.

Other characteristics of the microgranules according to the invention will become apparent on reading the examples which follow in which rotating turbomixers are preferably used, it also being possible to use any other coating machine, in particular one with a fluidized bed of the Glatt or Niro type, with the usual modifications known to those skilled in the art.

Example 1: Preparation of microgranules

1.1 Preparation of the mounting solution

The mounting excipients are weighed out in the following proportions:

PVP K 17* (povidone)	50% of the total DV
Sodium lauryl sulphate	25% of the total DV
Diethyl phthalate	25% of the total DV
Purified water	50% of the total S
95% ethyl alcohol	50% of the total S

* marketed by the company BASF

The 95% ethyl alcohol is poured into a first stainless steel mixer and the PVP K 17 is then introduced portionwise with stirring. Stirring is continued until the solution is homogeneous. An alcoholic 15% PVP K 17 solution is obtained.

The purified water is poured into a second stainless steel mixer and the sodium lauryl sulphate is then introduced portionwise with stirring. Stirring is continued until the solution is homogeneous. An aqueous 7.5% sodium lauryl sulphate solution is obtained.

The above two solutions are then mixed together and the diethyl phthalate is added with stirring.

1.2 Mounting of the Diltiazem

The support grains (sugar spheres) are placed in a rotating coating turbomixer. The active principle (hydrochloride) is mounted on the support grains by discontinuous spraying of the mounting suspension obtained above, in alternance with sequences of dusting of the active principle and sequences of leaving to stand. The dusting operation is repeated until the desired active principle content is obtained. The microgranules obtained are screened and are then dried.

Immediate-release microgranules of the following composition are obtained, the percentages being given on a weight basis:

Diltiazem	73.05%
support grains	22.55%
PVP K 17	2.20%
sodium lauryl sulphate	1.10%
diethyl phthalate	1.10%

for a Diltiazem (hydrochloride) content of 735.75 mg/g of microgranules.

1.3 Preparation of the coating solution

The following coating excipients are weighed out in the proportions indicated:

Eudragit RS 30 D*	DV* = 30.0% of the mass of Eudragit weighed out
Dibutyl sebacate	DV = 4.0% of the DV of Eudragit
Montanox 80 DF**	DV = 0.4% of the DV of Eudragit
Talc	DV = 20.0% of the DV of Eudragit
Triethyl citrate	DV = 16.0% of the DV of Eudragit
Purified water	S° = 50.0% of the mass of Eudragit weighed out

* marketed by the company Rhöm Pharma

DV* = dry varnish or dry extract (which remains after evaporation of the solvents)

** distributed by the company Seppic

S° = solvent in which the excipients are dissolved or diluted.

The purified water is poured into a stainless steel beaker and the Montanox 80 DF, the triethyl citrate and then the dibutyl sebacate are introduced portionwise with stirring. Stirring is continued until the solution is homogeneous, and the talc is then introduced portionwise with stirring. Lastly, the Eudragit RS 30 D is added with stirring being continued until the suspension is homogeneous and then throughout the coating phase.

1.4 Coating of microgranules

The microgranules obtained above are placed in a rotating coating turbomixer and they are then coated by continuous spraying of the solution obtained above. The mass of coated microgranules obtained is screened and they are then dried in a rotating turbomixer at room temperature, or by blowing with cold air if the room temperature is above 24°C.

This operational sequence is repeated as many times as required to obtain the desired kinetics.

Lastly, the SR microgranules obtained are lubricated by adding talc during the mixing phase.

Example 2

By carrying out the process described in Example 1, varying the amount of Eudragit RS 30 D and of excipients, microgranules with the compositions described in Table I below are obtained.

Table I

%	1	2	3	4	5	6	7	8	9
AP	55.56	62.17	51.92	55.81	61.49	45.1	50.37	50.50	54.12
N 30	17.08	19.19	16.03	17.23	18.98	13.92	15.55	15.59	16.71
PVP	1.86	1.87	1.56	1.98	1.85	1.36	1.52	1.52	1.63
LAS	0.93	0.94	0.78	0.84	0.93	0.68	0.76	0.76	0.81
DP	0.93	0.94	0.78	0.84	0.93	0.68	0.76	0.76	0.81
E RS	16.83	10.59	20.60	16.45	11.27	27.19	21.72	21.98	18.10
D S	2.73	0.42	0.83	0.66	0.44	1.12	0.88	0.88	0.72
M 80	0.07	0.05	0.08	0.07	0.05	0.11	0.09	0.09	0.08
Talc	2.85	2.13	4.12	3.79	2.25	5.47	4.86	4.39	4.11
TC	1.15	1.71	3.31	2.64	1.81	4.37	3.49	3.53	2.91
Total	100%								
mg/g	555.63	599.55	504.51	516.05	602.03	452.62	497.29	482.36	536.31

The percentages are given on a dry microgranule weight basis, with the following abbreviations:

AP = active principle - Diltiazem hydrochloride;

N 30 = neutral 30;

PVP = PVP K 17;

LAS = sodium lauryl sulphate;

DP = diethyl phthalate;

E RS = Eudragit RS 30 D;

DS = dibutyl sebacate;

M 80 = Montanox 80 DF;

TC = triethyl citrate;

mg/g = Diltiazem content in mg per g of SR microgranules.

Microgranules 4 consist of a mixture of microgranules 2 and 3, lubricated with 0.5% talc (% = weight of talc/weight of microgranules to be lubricated).

Microgranules 5 are obtained by a second coating of 400 g of microgranules 2 with the suspension of Example 1.1.

Microgranules 6 are obtained by a second coating of 500 g of microgranules 2 with the suspension of Example 1.1.

Microgranules 7 consist of a mixture of microgranules 5 and 6, lubricated with 0.5% talc.

Microgranules 8 are obtained by a second coating of 400 g of microgranules 2 with the suspension of Example 1.1.

Microgranules 9 consist of a mixture of microgranules 5 and 8, lubricated with 0.5% talc.

Example 3: Dissolution kinetics

The above microgranules are subjected to a study of the kinetics of dissolution in water over 24 hours. The results obtained are summarized in Table II below, expressed as a percentage of active principle in solution relative to the total active principle.

Table II

t(h)	1	2	3	4	5	6	7	8	9
2	2.2	12.7	0.8	4.9	3.1	1.2	2.1	1.1	1.7
4	29.6	82.9	1.1	36.4	37.0	1.4	19.9	1.7	20.2
6	-	94.1	1.4	41.1	85.7	1.9	38.0	1.8	36.5
8	-	97.2	1.9	42.2	90.8	2.3	39.9	2.1	38.2
10	-	98.8	3.8	43.6	92.8	2.6	40.9	2.5	39.0
12	50.6	100	30.9	56.2	94.1	3.0	41.5	3.2	39.7
14	63.3	-	74.8	82.8	94.9	3.4	42.0	18.7	45.5
16	-	-	88.9	92.0	95.4	4.4	43.6	63.7	68.3
18	94.4	-	93.7	95.0	95.7	12.5	50.7	84.6	83.4
20	-	-	96.5	96.7	96.0	55.7	65.9	91.0	88.1
22	-	-	-	97.7	96.1	85.2	80.7	94.4	90.3
24	98.0	-	-	98.7	-	-	92.3	-	91.5

Example 4: Bioequivalence with Cardizem® CD

The bioequivalence of gelatin capsules dosed with 300 mg of Diltiazem and containing the microgranules of composition 9 (Diltiazem CD) was compared in vivo with Cardizem® CD 300 mg marketed by the company Marion Merrell Dow Inc. in the United States.

The studies were carried out on three groups of

12 patients, by measuring the concentration of active principle in the plasma.

For the first group, the Cardizem® CD was administered on an empty stomach (reference).

For the second group, the Diltiazem CD was administered on an empty stomach ("test-fast").

For the third group, the Diltiazem CD was administered with simultaneous administration of a standardized meal, the American "breakfast" ("test-fed").

The average plasmatic concentration curves are reported in the appended Figure 1.

This study unequivocally recognizes the bioequivalence of Diltiazem CD according to the invention with Cardizem® CD, independently of the simultaneous taking of food.

Example 5: Preparation of bilayer microgranules

5.1 - Bilayer microgranules free of premounting solution (batch YED 006 x 1383.1)

A) Mounting of the first layer of Diltiazem, production of batch YED 006.

a) Preparation of the mounting solution

- Proportions of the excipients used:

PVP K 17	50% of the total DV*
SODIUM LAURYL SULPHATE	25% of the total DV
DIETHYL PHTHALATE	25% of the total DV
PURIFIED WATER	50% of the total S°
95% ETHYL ALCOHOL	50% of the total S

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

S° = solvents in which the excipients are dissolved or diluted.

- The solution is prepared in a stainless steel container,

- The 95% ethyl alcohol and then the purified water are poured into the container and then stirred,
- The PVP K 17 and then the lauryl sulphate are introduced successively and portionwise,
- Stirring is continued until the PVP K 17 and the lauryl sulphate are completely dissolved,
- The diethyl phthalate is then added and stirring is continued until the solution is homogeneous.

b) Mounting of the Diltiazem onto neutral support grains

- Neutral 30 support grains are placed in a rotating coating turbomixer,
- The active principle is mounted on the Neutral 30 grains by discontinuous spraying of the suspension described above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 0.85 to 1.18 mm,
- The microgranules are then dried in the rotating turbomixer
  * at room temperature and for 2 h 30 between two consecutive phases.
  * at 35°C and for 4 to 6 h for the final mounting phase of each day. After drying, the turbomixer is left rotating for 4 h without any heat being applied.
- The mass obtained is then lubricated with talc.

c) Formulation of the microgranules after mounting of the first layer of Diltiazem

Composition of the DV*	Amount in %
DILTIAZEM	74.17
NEUTRAL 30	21.26
PVP K 17	2.16
SODIUM LAURYL SULPHATE	1.08
DIETHYL PHTHALATE	1.08
TALC	0.24
Theoretical content	741.7 mg/g
Content obtained	735.9 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

B) Internal coating of the batch YED 006, production of batch YED 006 x 1383

a) Preparation of the coating suspension

- Portions of the excipients used:

AQUACOAT ECD 30	DV* = 30.0% of the mass of Aquacoat weighed out
DIBUTYL SEBACATE	DV = 24.0% of the DV of Aquacoat

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

- The suspension is prepared in a stainless steel container into which the Aquacoat ECD 30 is introduced,
- The dibutyl sebacate is introduced portionwise into the stirred Aquacoat,
- Stirring is continued until the suspension is homogeneous (about 15 minutes).

b) Internal coating of the Diltiazem microgranules

- The microgranules to be coated (obtained from batch YED 006) are placed in a coating turbomixer,

- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.25 mm,
- The microgranules are then dried in a rotating turbo-mixer at a temperature of 40°C for 2 h and then at room temperature for 7 h.

c) Formulation of batch YED 006 x 1383 after internal coating

Composition of the DV*	Amount in %
DILTIAZEM	56.61%
NEUTRAL 30	16.22%
PVP K 17	1.65%
SODIUM LAURYL SULPHATE	0.83%
DIETHYL PHTHALATE	0.83%
AQUACOAT BCD 30	19.10%
DIBUTYL SEBACATE	5.59%
TALC	0.18%
Theoretical content	566.1 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

C) Mounting of the second layer of Diltiazem on batch YED 006 x 1383, production of batch YED 006 x 1383.1

a) Preparation of the mounting solution

- Refer to paragraph A)a).

b) Mounting of the Diltiazem

- The active principle is mounted on the microgranules obtained after coating of the batch YED 006 x 1383, by discontinuous spraying of the suspension described

above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,

- The mass of microgranules obtained screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in the rotating turbomixer at room temperature for 8 h.

c) Formulation of the batch YED 006 x 1383.1 after mounting of the second layer of Diltiazem

Composition of the DV*	Amount in %
DILTIAZEM	67.14%
NEUTRAL 30	11.54%
PVP 17	2.17%
SODIUM LAURYL SULPHATE	1.09%
DIETHYL PHTHALATE	1.09%
AQUACOAT ECD 30	13.59%
DIBUTYL SEBACATE	3.26%
TALC	0.13%
Theoretical content	674.1 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

D) Outer coating of the batch YED 006 x 1383.1

a) Preparation of the coating suspension

- Proportions of the excipients used:

EUDRAGIT RS 30 D	DV* = 30.0% of the mass of Eudragit weighed out
DIBUTYL SEBACATE	DV = 4.0% of the DV of Eudragit
POLYSORBATE 80	DV = 0.4% of the DV of Eudragit
TRIETHYL CITRATE	DV = 16.0% of the DV of Eudragit
TALC	DV = 10.0% of the DV of Eudragit
PURIFIED WATER	S° = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

S° = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The Polysorbate 80, the triethyl citrate and the dibutyl sebacate (USP) are successively introdced portionwise into the stirred purified water,
- Stirring is continued until the solution is homogeneous (about 15 minutes),
- The Eudragit RS 30 D is then added,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the coating.

b) Outer coating of the Diltiazem microgranules

- The microgranules to be coated are placed in a coating turbomixer,
- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.40 mm,

- The microgranules are then dried in a rotating turbo-mixer at a temperature of 40°C for 1 h and then at 30°C for 8 h.

c) Formulation of batch YED 006 x 1383.1 after external coating

Composition of the DV*	Amount in %
DILTIAZEM	58.99%
NEUTRAL 30	10.14%
PVP K 17	1.91%
SODIUM LAURYL SULPHATE	0.95%
DIETHYL PHTHALATE	0.95%
EUDRAGIT RS 30 D	8.62%
AQUACOAT ECD 30	11.94%
DIBUTYL SEBACATE	3.22%
POLYSORBATE 80	0.04%
TALC	1.84%
TRIETHYL CITRATE	1.40%
Theoretical content	589.9 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

E) Results of dissolution after the internal coating, mounting of the second layer of Diltiazem and the external coating

YED 006 x 1383	YED 006 x 1381.1	YED 006 x 1383.1
Internal coating	Mounting of the second layer of Diltiazem	External coating
1h 1.38%	38.87%	0.68%
2h 9.45%	42.38%	1.82%
3h 20.33%	51.98%	8.49%
4h 28.82%	58.82%	28.41%
5h 34.99%	63.15%	37.67%
6h 39.84%	66.26%	41.68%
7h 43.92%	68.66%	45.31%
8h 47.37%	70.64%	48.64%
9h 50.58%	72.23%	51.51%
10h 53.27%	73.75%	54.00%
11h 55.77%	74.92%	56.12%
12h 57.96%	76.21%	58.23%
13h 59.96%	77.27%	59.89%
14h 61.94%	78.18%	61.63%
15h 63.62%	78.97%	63.14%
16h 65.30%	79.80%	64.56%
17h 66.62%	80.56%	66.06%
18h 68.25%	81.32%	67.42%
19h 69.52%	82.15%	68.78%
20h 70.79%	82.88%	70.21%
21h 71.95%	83.36%	71.57%
22h 73.12%		72.85%
23h 74.13%		74.02%
24h 75.10%		75.19%
Percentages of Diltiazem dissolved at each hour of sampling		

F) Formulations of batch YED 006 x 1383.1

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 006 x 1383.1
Mounting	
Active principle	80.87%
Neutral support	13.90%
Binder	2.61%
Surfactant	1.31%
Plasticizer	1.31%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 006 x 1383.1
Neutral support	10.14%
Mounting	
Active principle	58.99%
Binder	1.91%
Surfactant	0.95%
Plasticizer	0.95%
Coating	
Coating agent	20.56%
Bioavailability adjuvant	0.04%
Plasticizer	4.62%
Lubricant	1.84%

5.2 - Bilayer microgranules with protective coating solution

I - Batch YED 005B x 1350

A) Mounting of the first layer of Diltiazem, production of batch YED 005

a) Preparation of the mounting solution

• Refer to paragraph 5.1 A) a).

b) Mounting of Diltiazem on neutral support grains

• Refer to paragraph 5.1 A) b).

c) Formulation of batch YED 005 after mounting

Composition of the DV*	Amount in %
DILTIAZEM	74.65%
NEUTRAL 30	21.37%
PVP K 17	1.99%
SODIUM LAURYL SULPHATE	1.00%
DIETHYL PHTHALATE	1.00%
Theoretical content	746.50 mg/g
Content obtained	711.00 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

B) Internal coating of batch YED 005, production of batch YED 005 B

a) Preparation of the coating suspension

• Proportions of the excipients used:

EUDRAGIT RS 30 D	DV* = 30.0% of the mass of Eudragit weighed out
DIBUTYL SEBACATE	DV = 4.0% of the DV of Eudragit
POLYSORBATE 80	DV = 0.4% of the DV of Eudragit
TALC	DV = 10.0% of the DV of Eudragit
TRIETHYL CITRATE	DV = 16.0% of the DV of Eudragit
PURIFIED WATER	S° = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

S° = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The Polysorbate 80, the triethyl citrate and the dibutyl sebacate (USP) are introduced successively and portionwise into the stirred purified water,
- Stirring is continued until the solution is homogeneous (about 15 minutes),
- The Eudragit RS 30 D is then added,
- The talc is introduced portionwise into the suspension,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the coating,
- An amount of talc equivalent to that placed in suspension will be prepared in order to be dusted onto the mass during the coating,

b) Internal coating of the Diltiazem microgranules

- The microgranules to be coated (obtained from batch

YED 005) are placed in a perforated turbomixer,

- The microgranules are coated at a temperature of 30°C by continuous spraying of the suspension described above, in alternance with sequences of dusting with talc (amount identical to that placed in suspension),
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then dried in a rotating turbomixer at a temperature of 30°C for 1 h and then at 40°C for 2 h,
- The temperature is cooled to 30°C before carrying out a second screening through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then returned to the rotating turbomixer at a temperature of 30°C, throughout the period between the completed coating phase and the following one,
- This operation sequence is repeated until the desired kinetics are obtained,
- After the coating step, the microgranules are screened through a grille with a mesh size of 0.60 mm,
- They are then lubricated with an amount of talc equivalent to 0.75% of the coated mass obtained.

c) Formulation of batch YED 005 B after internal coating

Composition of the DV*	Amount in %
DILTIAZEM	53.20%
NEUTRAL 30	15.23%
PVP K 17	1.42%
SODIUM LAURYL SULPHATE	0.71%
DIETHYL PHTHALATE	0.71%
EUDRAGIT RS 30 D	19.96%
DIBUTYL SEBACATE	0.80%
POLYSORBATE 80	0.08%
TALC	4.70%
TRIETHYL CITRATE	3.19%
Theoretical content	532.0 mg/g
Content found	537.3 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

C) Premounting of batch YED 005 B, production of batch YED 005 B x 1350

a) Preparation of the premounting suspension

- Proportions of the excipients used:

EUDRAGIT L 30 D	DV* = 30.0% of the mass of Eudragit weighed out
TALC	DV = 10.0% of the DV of Eudragit
TRIETHYL CITRATE	DV = 10.0% of the DV of Eudragit
PURIFIED WATER	DV = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

S° = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- Triethyl citrate is introduced portionwise into the stirred purified water,
- Stirring is continued until the solution is homogeneous (about 15 minutes),
- The Eudragit L 30 D is then added,
- The talc is introduced portionwise into the suspension,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the premounting.

b) Premounting of the Diltiazem microgranules

- The microgranules to be coated (obtained from batch YED 005 B) are placed in a coating turbomixer,
- The microgranules are premounted by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in a rotating turbomixer at a temperature of 40°C for 1 h and then at room temperature for 7 h.

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c) Formulation of batch YED 005 B x 1350 after protective coating

Composition of the DV*	Amount in %
DILTIAZEM	50.19%
NEUTRAL 30	14.36%
PVP K 17	1.34%
SODIUM LAURYL SULPHATE	0.67%
DIETHYL PHTHALATE	0.67%
EUDRAGIT RS 30 D	18.83%
EUDRAGIT L 30 D	4.72%
DIBUTYL SEBACATE	0.75%
POLYSORBATE 80	0.08%
TALC	4.91%
TRIETHYL CITRATE	3.19%
Theoretical content	501.9 mg/g
Content found	521.0 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

D) Mounting of the second layer of Diltiazem on batch YED 005 B x 1350

a) Preparation of the mounting solution

- Refer to paragraph 5.1 A) a)

b) Mounting of the Diltiazem

- The active principle is mounted on microgranules obtained from the premounting, by discontinuous spraying of the suspension described above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,

- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in the rotating turbomixer at room temperature for 8 h.

c) Formulation of batch YED 005 x 1350 after mounting of the second layer of Diltiazem

Composition of the DV*	Amount in %
DILTIAZEM	61.40%
NEUTRAL 30	10.60%
PVP K 17	1.91%
SODIUM LAURYL SULPHATE	0.95%
DIETHYL PHTHALATE	0.95%
EUDRAGIT RS 30 D	13.90%
EUDRAGIT L 30 D	3.48%
DIBUTYL SEBACATE	0.56%
POLYSORBATE 80	0.06%
TALC	3.62%
TRIETHYL CITRATE	2.57%
Theoretical content	614.0 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

E) External coating of batch YED 005 B x 1350

a) Preparation of the coating suspension

- Proportions of the excipients used:

EUDRAGIT RS 30 D	DV* = 30.0% of the mass of Eudragit weighed out
DIBUTYL SEBACATE	DV = 4.0% of the DV of Eudragit
POLYSORBATE 80	DV = 0.4% of the DV of Eudragit
TRIETHYL CITRATE	DV = 16.0% of the DV of Eudragit
TALC	DV = 10.0% of the DV of Eudragit
PURIFIED WATER	DV = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

S° = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The Polysorbate 80, the triethyl citrate and the dibutyl sebacate (USP) are successively introduced portionwise into the stirred purified water,
- Stirring is continued until the solution is homogeneous (about 15 minutes),
- The Eudragit RS 30 D is then added,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the coating.

b) External coating of the Diltiazem microgranules

- The microgranules to be coated are placed in a coating turbomixer,
- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,

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- The microgranules are then dried in a rotating turbo-mixer at a temperature of 40°C for 1 h and then at room temperature for 7 h.

c) Formulation of batch YED 005 B x 1350 after external coating

Composition of the DV*	Amount in %
DILTIAZEM	53.28%
NEUTRAL 30	9.20%
PVP K 17	1.65%
SODIUM LAURYL SULPHATE	0.83%
DIETHYL PHTHALATE	0.83%
EUDRAGIT RS 30 D	21.48%
EUDRAGIT L 30 D	3.02%
DIBUTYL SEBACATE	0.86%
POLYSORBATE 80	0.08%
TALC	5.03%
TRIETHYL CITRATE	3.74%
Theoretical content	532.8 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

F) Results of dissolution after the internal coating, mounting of the second layer of Diltiazem and the external coating

YED 005 B	YED 005 B x 1350	YED 005 B x 1350
Internal coating	Mounting of the second layer of Diltiazem	External coating
1h 0.23%	13.11%	1.90%
2h 0.51%	34.61%	10.53%
3h 0.65%	36.33%	35.30%
4h 0.83%	37.55%	38.56%
5h 0.93%	38.78%	41.59%
6h 0.97%	40.03%	44.92%
7h 1.25%	41.29%	48.11%
8h 1.53%	42.63%	51.59%
9h 2.31%	44.12%	55.45%
10h 4.44%	45.82%	59.30%
11h 9.02%	47.93%	63.07%
12h 17.11%	50.71%	67.30%
13h 28.43%	54.39%	71.45%
14h 42.29%	58.89%	75.45%
15h 55.17%	63.93%	78.63%
16h 64.91%	69.10%	81.57%
17h 71.75%	74.04%	84.01%
18h 76.41%	78.45%	86.43%
19h 79.59%	82.02%	
20h 81.65%	84.85%	
21h 83.31%	86.97%	
22h 84.69%	88.66%	
23h 85.85%	89.94%	
24h 86.81%	90.98%	
Percentages of Diltiazem dissolved at each hour of sampling		

G) Formulations of batch YED 005 B x 1350

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 005 B x 1350
Mounting	
Active principle	80.99%
Neutral support	13.98%
Binder	2.52%
Surfactant	1.26%
Plasticizer	1.26%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 005 B x 1350
Neutral support	9.20%
Mounting	
Active principle	53.28%
Binder	1.65%
Surfactant	0.83%
Plasticizer	0.83%
Coating	
Coating agent	24.50%
Bioavailability adjuvant	0.08%
Plasticizer	4.60%
Lubricant	5.03%

II - Batch YED 006 x 1392.2

A) Mounting of the first layer of Diltiazem, production

of batch YED 006

a) Preparation of the mounting solution

- Refer to paragraph 5.1 A) a).

b) Mounting of the Diltiazem on neutral support grains

- Refer to paragraph 5.1 A) b),
- The mass obtained is then lubricated with talc.

c) Formulation of batch YED 006 after mounting of the first layer of Diltiazem

- Refer to paragraph 5.1 B) a).

B) Internal coating of batch YED 006, production of batch YED 006 B

a) Preparation of the coating suspension

- Refer to paragraph 5.2 B) a).

b) Internal coating of the Diltiazem microgranules (first step)

- The microgranules to be coated (obtained from batch YED 006) are placed in a perforated turbomixer,
- The microgranules are coated at a temperature of 30°C by continuous spraying of the suspension described above, in alternance with sequences of dusting with talc (amount identical to that placed in suspension),
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then dried in a rotating turbomixer at a temperature of 30°C for 1 h and then at 40°C for 2 h,
- The temperature is returned to 30°C before carrying out a second screening through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then returned to the rotating turbomixer at a temperature of 30°C, throughout the period between the completed coating phase and the following one,
- This operational sequence is repeated until the

desired kinetics are obtained,

- After the coating step, the microgranules are screened through a grille with a mesh size of 0.60 mm,
- They are then lubricated with an amount of talc equivalent to 0.75% of the coated mass obtained.

c) Formulation of batch YED 006 B after internal coating

Composition of the DV*	Amount in %
DILTIAZEM	69.18%
NEUTRAL 30	19.83%
PVP K 17	2.02%
SODIUM LAURYL SULPHATE	1.01%
DIETHYL PHTHALATE	1.01%
EUDRAGIT RS 30 D	4.66%
DIBUTYL SEBACATE	0.19%
POLYSORBATE 80	0.02%
TALC	1.35%
TRIETHYL CITRATE	0.75%
Theoretical content	691.8 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

C) Internal coating of batch YED 006 B, production of batch YED 006 B x 1392

a) Preparation of the coating suspension

- Refer to paragraph 5.1 B) a).

b) Internal coating of the Diltiazem microgranules (second step)

- The microgranules to be coated (obtained from batch YED 006 B) are placed in a perforated turbomixer,

- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through the grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then dried in a rotating turbo-mixer at a temperature of 30°C for 1 h and then at 40°C for 2 h,
- The temperature is returned to 30°C before carrying out a second screening through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then returned to the rotating turbomixer at a temperature of 30°C, throughout the period between the completed coating phase and the following one,
- This operational sequence is repeated until the desired kinetics are obtained,
- After the coating step, the microgranules are screened through a grille with a mesh size of 0.60 mm,

c) Formulation of batch YED 006 B x 1392 after internal coating

Composition of the DV*	Amount in %
DILTIAZEM	52.29%
NEUTRAL 30	14.99%
PVP K 17	1.53%
SODIUM LAURYL SULPHATE	0.76%
DIETHYL PHTHALATE	0.76%
EUDRAGIT RS 30 D	20.91%
DIBUTYL SEBACATE	0.84%
POLYSORBATE 80	0.08%
TALC	4.49%
TRIETHYL CITRATE	3.35%
Theoretical content	522.9 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

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D) Premounting of batch YED 006 B x 1392, production of batch YED 006 B x 1392.2

a) Preparation of the premounting suspension

- Proportions of the excipients used:

EUDRAGIT L 30 D	DV* = 30.0% of the mass of Eudragit weighed out
TRIETHYL CITRATE	DV = 10.0% of the DV of Eudragit
PURIFIED WATER	DV = 20.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

°S = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The triethyl citrate is introduced portionwise into the stirred purified water,
- Stirring is continued until the solution is homogeneous (about 15 minutes),
- The Eudragit L 30 D is then added,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the premounting.

b) Premounting of the Diltiazem microgranules

- The microgranules to be coated are placed in a perforated turbomixer,
- The microgranules are premounted at a tempertare of 30°C by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.40 mm,
- The microgranules are then dried in a rotating turbo-

mixer at a temperature of 35°C for 10 h.

c) Formulation of batch YED 006 B x 1392.2 after pre-mounting

Composition of the DV*	Amount in %
DILTIAZEM	50.19%
NEUTRAL 30	14.36%
PVP K 17	1.34%
SODIUM LAURYL SULPHATE	0.67%
DIETHYL PHTHALATE	0.67%
EUDRAGIT RS 30 D	18.83%
EUDRAGIT L 30 D	4.72%
DIBUTYL SEBACATE	0.75%
POLYSORBATE 80	0.08%
TALC	4.91%
TRIETHYL CITRATE	3.19%
Theoretical content	501.9 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

E) Mounting of the second layer of Diltiazem on batch YED 006 B x 1392.2

a) Preparation of the mounting solution

- Refer to paragraph 5.2 A) a).

b) Mounting of the Diltiazem

- The active principle is mounted on the microgranules obtained from the protective coating of batch YED 006 B x 1392.2, by discontinuous spraying of the suspension described above, in alternance with sequences of dusting of the Diltiazem and sequences of

leaving to stand,

- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in the rotating turbomixer at room temperature for 8 h.

c) Formulation of batch YED 006 B x 13912.2 after mounting of the second layer of Diltiazem

Composition of the DV*	Amount in %
DILTIAZEM	58.75%
NEUTRAL 30	10.11%
PVP K 17	1.85%
SODIUM LAURYL SULPHATE	0.93%
DIETHYL PHTHALATE	0.92%
EUDRAGIT RS 30 D	14.11%
EUDRAGIT L 30 D	6.75%
DIBUTYL SEBACATE	0.56%
POLYSORBATE 80	0.06%
TALC	3.03%
TRIETHYL CITRATE	2.93%
Theoretical content	587.5 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

F) External coating of batch YED 006 B x 1392.2

a) Preparation of the coating suspension

- Refer to paragraph 5.2 B) a).

b) External coating of the Diltiazem microgranules

- The microgranules to be coated are placed in a perforated turbomixer,

- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then dried in a rotating turbomixer at a temperature of 30°C for 1 h and then 40°C for 2 h,
- The temperature is returned to 30°C before carrying out a second screening through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then returned to the rotating turbomixer at a temperature of 30°C, throughout the period between the completed coating phase and the following one,
- This operational sequence is repeated until the desired kinetics are obtained,
- After the coating step, the microgranules are screened through a grille with a mesh size of 0.60 mm,
- They are then lubricated with an amount of talc equivalent to 1.5% of the coated mass obtained.

c) Formulation of batch YED 006 B x 1392.2 after external coating

Composition of the DV*	Amount in %
DILTIAZEM	49.71%
NEUTRAL 30	8.56%
PVP K 17	1.57%
SODIUM LAURYL SULPHATE	0.78%
DIETHYL PHTHALATE	0.78%
EUDRAGIT RS 30 D	21.89%
EUDRAGIT L 30 D	5.71%
DIBUTYL SEBACATE	0.88%
POLYSORBATE 80	0.09%
TALC	5.97%
TRIETHYL CITRATE	4.08%
Theoretical content	497.1 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

G) Results of dissolution after internal coating and external coating (in two media)

H_2O medium		H_2O media pH 7	
YED 006 B x 1392		YED 006 B x 1392.2	
Internal coating		External coating	
1h	0.61%	1.08%	1.46%
2h	0.84%	3.37%	5.60%
3h	0.99%	12.73%	16.72%
4h	1.14%	25.42%	21.59%
5h	1.29%	31.93%	22.82%
6h	1.44%	34.07%	23.43%
7h	1.67%	35.09%	23.85%
8h	1.90%	35.78%	24.31%
9h	2.66%	36.47%	24.62%
10h	4.63%	37.02%	25.04%
11h	10.38%	37.42%	25.53%
12h	22.73%	37.96%	26.07%
13h	40.08%	38.41%	26.83%
14h	57.50%	38.93%	27.71%
15h	71.26%	39.39%	28.93%
16h	80.11%	39.79%	30.34%
17h	85.78%	40.17%	32.39%
18h	89.03%	40.62%	35.14%
19h	91.07%	41.22%	38.47%
20h	92.65%	41.77%	42.07%
21h	93.65%	42.38%	45.81%
22h		43.22%	49.47%
23h		43.84%	52.74%
24h		44.74%	55.79%
Percentages of Diltiazem dissolved at each hour of sampling			

H) Formulations of batch YED 006 x 1392.2

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 006 x 1392.2
Mounting	
Active principle	80.96%
Neutral support	13.93%
Binder	2.55%
Surfactant	1.28%
Plasticizer	1.27%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 006 x 1392.2
Neutral support	8.56%
Mounting	
Active principle	49.71%
Binder	1.57%
Surfactant	0.78%
Plasticizer	0.78%
Coating	
Coating agent	27.59%
Bioavailability adjuvant	0.09%
Plasticizer	4.96%
Lubricant	5.97%

EXAMPLE 6 - Preparation of monolayer microgranules

A) Mounting of the Diltiazem, production of batch YED 001

a) Preparation of the mounting solution

- Proportions of the excipients used:

PVP K 17	50% of the total DV*	DV =	15% of the weight of the solution
SODIUM LAURYL SULPHATE	25% of the total DV		
DIETHYL PHTHALATE	25% of the total DV		
PURIFIED WATER	50% of the total S°	S =	85% of the weight of the solution
95% ETHYL ALCOHOL	50% of the total S		

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

°S = solvents in which the excipients are dissolved or diluted.

- The solution is prepared in a stainless steel container,
- The 95% ethyl alcohol and then the purified water are poured into the container and then stirred,
- The PVP K 17 and then the lauryl sulphate are successively introduced portionwise,
- Stirring is continued until the PVP K 17 and the lauryl sulphate have completely dissolved,
- The diethyl phthalate is then added and stirring is continued until the solution is homogeneous.

b) Mounting of the Diltiazem on the neutral support grains

- Neutral 30 support grains are placed in a rotating coating turbomixer,
- The active principle is mounted on the Neutral 30 grains by discontinuous spraying of the solution described above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 0.71 to 1.00 mm,

- The microgranules are then dried in the rotating turbomixer at room temperature for 3 to 8 h.

c) Formulation of batch YED 001 after mounting

Composition of the DV*	Amount in %
DILTIAZEM	73.05%
NEUTRAL 30	22.55%
PVP K 17	2.20%
SODIUM LAURYL SULPHATE	1.10%
DIETHYL PHTHALATE	1.10%
Theoretical content	730.50 mg/g
Content obtained	735.75 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

B) Coating of batch YED 001, production of batches YED 001 A1 and YED 001 B1

After separation of the mass of microgranules obtained on mounting (proportions: 45%/55% w/w), the two masses are coated separately with different amounts of excipients.

a) Preparation of the coating suspension

- Proportions of the excipients used:

EUDRAGIT RS 30 D	DV* = 30.0% of the mass of Eudragit weighed out
DIBUTYL SEBACATE	DV = 4.0% of the DV of Eudragit
Polysorbate 80	DV = 0.4% of the DV of Eudragit
TRIETHYL CITRATE	DV = 16.0% of the DV of Eudragit
TALC	DV = 10.0% of the DV of Eudragit
PURIFIED WATER	S° = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

°S = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The Polysorbate 80, the triethyl citrate and the dibutyl sebacate (USP) are successively introduced portionwise into the stirred purified water,
- Stirring is continued until the suspension is homogeneous (about 15 minutes),
- The Eudragit RS 30 D and the talc are then added,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the coating.

b) Coating of the Diltiazem microgranules

- The microgranules to be coated (obtained from batch YED 001) are placed in a coating turbomixer,
- The microgranules are coated at a temperature of 30°C by continuous spraying of the suspension described above, in alternance with sequences of dusting with talc (DV=20% of the DV of Eudragit),
- The mass of microgranules obtained is screened through a grille with a mesh size ranging from 1.00 to 1.12 mm,
- The microgranules are then dried in a rotating turbomixer at room temperature, throughout the period between the completed coating phase and the following one,
- This operational sequence is repeated until the desired kinetics for batches A1 and B1 are obtained.

c) Formulation of batches YED 001 A1 and YED 001 B1 after coating, YED 001 M3 mixture

- After the coating steps, a fraction of the granules obtained from batch YED 001 A1 and a fraction of the granules obtained from batch YED 001 B1 are mixed together and lubricated with talc (DV of talc = 0.50%

of the total mass mixed),

- The mixture is made such that the amount of active principle provided by batch YED 001 A1 is equal to 40% of the total amount of active principle in the mixture. The remaining 60% are provided by batch YED 001 B1.

Batch	YET 001A1	YED 001B1	YED 001M3
Composition of the DV*	Amount in %		
DILTIAZEM	61.5%	45.1%	50.4%
NEUTRAL 30	19.0%	13.9%	15.5%
PVP K 17	1.9%	1.4%	1.5%
SODIUM LAURYL SULPHATE	0.9%	0.7%	0.8%
DIETHYL PHTHALATE	0.9%	0.7%	0.8%
EUDRAGIT RS 30 D	11.3%	27.2%	21.7%
DIBUTYL SEBACATE	0.4%	1.1%	0.9%
POLYSORBATE 80	0.1%	0.1%	0.1%
TALC	2.3%	5.5%	4.9%
TRIETHYL CITRATE	1.8%	4.4%	3.5%
Theoretical content	615mg/g	451mg/g	504mg/g
Content found	602mg/g	453mg/g	497mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

C) Results of dissolution of batches YED 001A1, YED 001B1, YED 001M3, 8175 (gelatin capsules of batch YED 001M3 containing a 300 mg dose)

	YED 001 A1	YED 001B1	YED 001M3	8175 (YED 001M3)
1h	0.60%	0.75%	0.50%	1.01%
2h	3.06%	1.20%	2.10%	3.36%
3h	10.69%	1.27%	6.70%	12.37%
4h	37.01%	1.42%	19.90%	26.77%
5h	72.92%	1.71%	33.80%	37.05%
6h	85.68%	1.93%	38.00%	40.37%
7h	89.04%	2.15%	39.20%	41.49%
8h	90.77%	2.29%	39.90%	42.19%
9h	91.97%	2.43%	40.50%	42.69%
10h	92.79%	2.57%	40.90%	43.10%
11h	93.61%	2.72%	41.20%	43.62%
12h	49.14%	3.00%	41.50%	44.18%
13h	94.53%	3.21%	41.70%	44.72%
14h	94.90%	3.43%	42.00%	45.30%
15h	95.12%	3.78%	42.50%	46.06%
16h	95.35%	4.43%	43.60%	46.81%
17h	95.50%	6.24%	45.60%	47.91%
18h	95.65%	12.46%	50.70%	50.80%
19h	95.73%	31.04%	58.00%	57.72%
20h	95.95%	55.72%	65.90%	69.03%
21h	96.03%	75.14%	73.20%	81.44%
22h	96.10%	85.19%	80.70%	90.49%
23h			87.50%	95.46%
24h			92.30%	98.12%

Percentages of Diltiazem dissolved at each hour of sampling

D) Formulations of batch YED 001 M3

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 001 M3
Mounting	
Active principle	73.05%
Neutral support	22.55%
Binder	2.20%
Surfactant	1.10%
Plasticizer	1.10%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 001 M3
Neutral support	15.55
Mounting	
Active principle	50.37%
Binder	1.52%
Surfactant	0.76%
Plasticizer	0.76%
Coating	
Coating agent	21.72%
Bioavailability adjuvant	0.09%
Plasticizer	4.37%
Lubricant	4.86%

EXAMPLE 7 - Preparation of monolayer microgranules

A) Mounting of Diltiazem, production of batches YED 004 and YED 005

a) Preparation of the mounting soultion

- Proportions of the excipients used:

PVP K 17	50% of the total DV*	
SODIUM LAURYL SULPHATE	25% of the total DV	DV = 20% of the weight of the solution
DIETHYL PHTHALATE	25% of the total DV	
PURIFIED WATER	50% of the total S°	S = 20% of the weight of the solution
95% ETHYL ALCOHOL	50% of the total S	

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

°S = solvent in which the excipients are dissolved or diluted.

- The solution is prepared in a stainless steel container,
- The 95% ethyl alcohol and then the purified water are poured into the container and then stirred,
- The PVP K 17 and then the lauryl sulphate are successively introduced portionwise,
- Stirring is continued until the PVP K 17 and the lauryl sulphate have completely dissolved,
- The diethyl phthalate is then added and stirring is continued until the solution is homogeneous.

b) Mounting of the Diltiazem on the neutral support grains

- Neutral 30 support grains are placed in a rotating coating turbomixer,
- The active principle is mounted on the Neutral 30 grains by discontinuous spraying of the suspension described above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,
- The mass of microgranules obtained is screened through

a grille with a mesh size ranging from 0.85 to 1.18 mm,

- The microgranules are then dried in the rotating turbomixer.
  - * YED 004: at 35°C for 12 to 14 h,
  - * YED 005: · At room temperature for 2 h 30 between two consecutive phases.
    · At 35°C for 4 to 6 h for the final mounting phase of each day.
    · After drying, the turbomixer is left rotating for 4 h without any heat being supplied.

c) Formulation of batches YED 004 and YED 005 after mounting

BATCH	YED 004	YED 005
Composition of the DV*	Amount in %	Amount in %
DILTIAZEM	73.94	74.65
NEUTRAL 30	21.20	21.37
PVP K 17	2.43	1.99
SODIUM LAURYL SULPHATE	1.21	1.00
DIETHYL PHTHALATE	1.21	1.00
THEORETICAL CONTENT	739.4 mg/g	746.5 mg/g
CONTENT OBTAINED	727.8 mg/g	711.0 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

B) Coating of batches YED 004 and YED 005, production of batches YED 004A and YED 005B

After separation of the masses of microgranules obtained on mounting (proportions: 40%/60% w/w), two of the masses YED 004A (40% of YED 004) and YED 005B (60% of YED 005) are coated separately with different amounts of

excipients.

a) Preparation of the coating suspension

- Proportions of the excipients used:

EUDRAGIT RS 30 D	DV* = 30.0% of the mass of Eudragit weighed out
DIBUTYL SEBACATE	DV = 4.0% of the DV of Eudragit
Polysorbate 80	DV = 0.4% of the DV of Eudragit
TALC	DV = 10.0% of the DV of Eudragit
TRIETHYL CITRATE	DV = 16.0% of the DV of Eudragit
PURIFIED WATER	S° = 50.0% of the mass of Eudragit weighed out

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

°S = solvent in which the excipients are dissolved or diluted.

- The suspension is prepared in a stainless steel container into which the purified water is introduced,
- The Polysorbate 80, the triethyl citrate and the dibutyl sebacate (USP) are successively introduced portionwise into the stirred purified water,
- Stirring is continued until the suspension is homogeneous (about 15 minutes),
- The Eudragit RS 30 D is then added,
- The talc is introduced portionwise into the suspension,
- Stirring is continued until the mixture is homogeneous (about 15 minutes) and then throughout the coating,

b) Coating of the Diltiazem microgranules

- The microgranules to be coated (obtained from batches YED 004 and YED 005) are placed in a perforated turbomixer,
- The microgranules are coated at a temperature of 30°C by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through

a grille with a mesh size ranging from 1.18 to 1.25 mm,

- The microgranules are then dried in a rotating turbomixer at a temperature of 30°C for 1 h and then at 40°C for 2 h,
- The temperature is returned to 30°C before carrying out a second screening through a grille with a mesh size ranging from 1.18 to 1.25 mm,
- The microgranules are then returned to the rotating turbomixer at a temperature of 30°C, throughout the period between the completed coating phase and the following one,
- This operational sequence is repeated until the desired kinetics are obtained,
- After the coating step, the microgranules are screened through a grille with a mesh size of 0.60 mm,
- They are then lubricated with an amount of talc equivalent to 0.75% of the coated mass obtained.

c) Formulation of batches YED 004A and YED 005B after coating, YED 005M mixture

- A fraction of the granules obtained from batch YED 004A and a fraction of the granules obtained from batch YED 005B are mixed together,
- The mixture is made such that the amount of active principle provided by batch YED 004A is equal to 40% of the total amount of active principle in the mixture. The remaining 60% are provided by batch YED 005B.

BATCH	YED 004A	YED 005B	YED 005M
Composition of the DV*	Amount in %	Amount in %	Amount in %
DILTIAZEM	65.37	53.20	57.43
NEUTRAL 30	18.75	15.23	16.45
PVP K 17	2.15	1.42	1.68
SODIUM LAURYL SULPHATE	1.07	0.71	0.84
DIETHYL PHTHALATE	1.07	0.71	0.84
EUDRAGIT RS 30 D	7.74	19.96	15.67
DIBUTYL SEBACATE	0.31	0.80	0.63
POLYSORBATE 80	0.04	0.08	0.07
TALC	2.27	4.70	3.91
TRIETHYL CITRATE	1.24	3.19	2.51
THEORETICAL CONTENT	654 mg/g	532 mg/g	574 mg/g
CONTENT FOUND	656 mg/g	537 mg/g	540 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

C) Results of dissolution of batches YED 004A, YED 005B, YED 005M, 8394 (gelatin capsules of batch YED 005M containing a 300 mg dose)

	YED 004A	YED 005B	YED 005M	8394
1h	3.99	0.26	2.15	2.31
2h	11.32	0.56	6.25	6.85
3h	32.46	0.72	16.70	19.15
4h	65.74	0.92	30.03	33.44
5h	85.57	1.02	35.81	39.44
6h	92.79	1.07	37.60	41.49
7h	95.83	1.38	38.52	42.54
8h	97.58	1.69	39.18	43.24
9h	99.07	2.55	39.84	43.98
10h	100.21	4.90	40.61	44.83
11h	100.98	9.96	42.40	46.23
12h	101.80	18.90	45.62	48.74
13h	102.26	31.41	51.18	52.71
14h	102.77	46.73	58.46	58.53
15h	103.08	60.96	67.33	65.63
16h	103.23	71.72	75.60	73.50
17h	103.70	79.27	82.28	80.27
18h	103.69	84.42	87.18	85.46
19h	103.90	87.94	90.44	89.21
20h	103.90	90.21	92.66	97.88
21h	103.90	92.05	94.39	93.75
22h	103.95	93.58	95.67	95.15
23h	103.89	94.85	96.73	96.30
24h	103.94	95.92	97.70	97.29

Percentages of Diltiazem dissolved at each hour of sampling

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D) Formulations of batch YED 005 M

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 005 M
Mounting	
Active principle	74.37%
Neutral support	21.30%
Binder	2.17%
Surfactant	1.08%
Plasticizer	1.08%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 005 M
Neutral support	16.45%
Mounting	
Active principle	57.43%
Binder	1.68%
Surfactant	0.84%
Plasticizer	0.84%
Coating	
Coating agent	15.67%
Bioavailability adjuvant	0.07%
Plasticizer	3.13%
Lubricant	3.91%

EXAMPLE 8 - Preparation of bilayer microgranules

A) Mounting of the first layer of Diltiazem, production

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of batch YED 005

- Refer to paragraph A) of Example 8.

B) Internal coating of batch YED 005, production of batch YED 005 x 1406

a) Preparation of the coating suspension

- Refer to paragraph B) a) of Example 8.

b) Internal coating of the Diltiazem microgranules

- The microgranules to be coated are placed in a coating turbomixer,
- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in a rotating turbo-mixer at a temperature of 40°C for 2 h.

c) Formulation of batch YED 005 x 1406 after internal coating

Composition of the DV*	Amount in %
DILTIAZEM	58.12
NEUTRAL 30	16.63
PVP K 17	1.55
SODIUM LAURYL SULPHATE	0.78
DIETHYL PHTHALATE	0.78
EUDRAGIT RS 30 D	15.61
DIBUTYL SEBACATE	0.62
POLYSORBATE 80	0.06
TALC	3.35
TRIETHYL CITRATE	2.50
THEORETICAL CONTENT	581.2 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

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C) Premounting of batch YED 005 x 1406

a) Preparation of the premounting suspension

- Refer to paragraph II D) a) of Example 5.2.

b) Premounting of the Diltiazem microgranules

- The microgranules to be premounted are placed in a coating turbomixer,
- The microgranules are premounted at a temperature of 30°C by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in a rotating turbo-mixer at a temperature of 35°C for 2 h.

c) Formulation of batch YED 005 x 1406 after premounting

Composition of the DV*	Amount in %
DILTIAZEM	52.36
NEUTRAL 30	14.98
PVP K 17	1.40
SODIUM LAURYL SULPHATE	0.70
DIETHYL PHTHALATE	0.70
EUDRAGIT RS 30 D	14.06
EUDRAGIT L 30 D	9.01
DIBUTYL SEBACATE	0.56
POLYSORBATE 80	0.06
TALC	3.02
TRIETHYL CITRATE	3.16
THEORETICAL CONTENT	523.6 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

D) Mounting of the second layer of Diltiazem on batch YED 005 x 1406

a) Preparation of the mounting solution

- Refer to paragraph A) a) of Example 8.

b) Mounting of the Diltiazem

- The active principle is mounted on microgranules obtained from the protective coating of batch YED 005 x 1406, by discontinuous spraying of the suspension described above, in alternance with sequences of dusting of the Diltiazem and sequences of leaving to stand,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.60 to 1.80 mm,
- The microgranules are then dried in the rotating turbomixer at room temperature for 12 h.

c) Formulation of batch YED 005 x 1406 after mounting of the second layer of Diltiazem

Composition of the DV*	Amount in %
DILTIAZEM	62.58
NEUTRAL 30	11.08
PVP K 17	2.13
SODIUM LAURYL SULPHATE	1.06
DIETHYL PHTHALATE	1.06
EUDRAGIT RS 30 D	10.40
EUDRAGIT L 30 D	6.66
DIBUTYL SEBACATE	0.41
POLYSORBATE 80	0.04
TALC	2.23
TRIETHYL CITRATE	2.33
THEORETICAL CONTENT	625.8 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

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E) External coating of batch YED 005 x 1406

a) Preparation of the coating suspension

- Refer to paragraph B) a) of Example 8.

b) External coating of the Diltiazem microgranules

- The microgranules to be coated are placed in a coating turbomixer,
- The microgranules are coated by continuous spraying of the suspension described above,
- The mass of microgranules obtained is screened through a grille with a mesh size of 1.50 mm,
- The microgranules are then dried in a rotating turbomixer at a temperature of 40°C for 1 h and then at room temperature for 7 h.

c) Formulation of batch YED 005 x 1406 after external coating

Composition of the DV*	Amount in %
DILTIAZEM	55.46
NEUTRAL 30	9.82
PVP K 17	1.88
SODIUM LAURYL SULPHATE	0.94
DIETHYL PHTHALATE	0.94
EUDRAGIT RS 30 D	16.30
EUDRAGIT L 30 D	5.91
DIBUTYL SEBACATE	0.65
POLYSORBATE 80	0.07
TALC	4.82
TRIETHYL CITRATE	3.20
THEORETICAL CONTENT	554.6 mg/g

DV* = dry varnish or dry extract (which remains after evaporation of the solvents).

F) Results of dissolution after internal coating and external coating (in two media)

F) Results of dissolution after internal coating and external coating (in two media)

	YED 005 x 1406	YED 005 x 1406	YED 005 x 1406	YED 005 x 1406	YED 005 x 1406	YED 005 x 1406
	Internal coating (in %)	Premounting (in %)	External coating (in %)	Premounting (in %)	Mounting of the second layer of Diltiazem (in %)	External coating (in %)
	H_2O			pH 7		
1h	0.08	0.35	7.35	0.40	39.51	16.72
2h	0.35	0.46	32.78	0.66	39.67	31.36
3h	0.53	0.51	36.32	0.81	39.76	32.44
4h	0.70	0.55	37.09	1.01	39.85	32.61
5h	1.20	0.61	37.39	1.21	39.93	32.84
6h	2.53	0.66	37.76	1.61	40.15	33.13
7h	5.96	0.70	38.06	2.42	40.45	33.36
8h	15.30	0.81	38.17	6.81	40.77	33.93
9h	38.46	1.06	38.41	21.45	41.83	34.84
10h	67.09	1.91	38.72	39.58	44.51	36.50
11h	84.19	5.19	39.04	51.16	50.59	39.63
12h	91.67	13.24	39.63	57.65	62.44	44.44
13h	95.19	22.93	40.53	62.19	75.44	50.52

14h	97.22	30.22	41.72	65.61	83.95	56.66
15h	98.59	35.49	43.21	68.12	87.96	62.41
16h	99.99	35.96	44.99	70.28	89.97	67.04
17h	100.84	42.77	46.91	71.89	90.94	70.91
18h	101.59	45.36	49.49	73.18	91.69	74.04
9h	102.34	47.84	52.20	74.75	92.29	76.36
20h	102.89	50.05	55.51	75.80	92.95	78.34
21h	103.34	51.88	58.72	76.84	93.40	79.91
22h	103.81	53.78	62.01	77.69	93.78	81.11
23h	104.29	55.59	65.15	78.70	94.14	82.28
24h	104.69	57.19	68.06	79.50	94.37	83.04
	Percentage of Diltiazem dissolved at each hour of sampling					

G) Formulations of batch YED 005 x 1406

- percentages given on a weight basis for a total of 100 (excluding coating):

	YED 005 x 1406
Mounting	
Active principle	80.32%
Neutral support	14.22%
Binder	2.73%
Surfactant	1.36%
Plasticizer	1.36%

- percentage on a dry weight basis for a total of 100% (final composition):

	YED 005 x 1406
Neutral support	9.82%
Mounting	
Active principle	55.46%
Binder	1.88%
Surfactant	0.94%
Plasticizer	0.94%
Coating	
Coating agent	22.21%
Bioavailability adjuvant	0.07%
Plasticizer	3.85%
Lubricant	4.82%

CLAIMS

1. Sustained-release (SR) microgranules containing Diltiazem, characterized in that they comprise:

- a neutral granular support coated with an active layer comprising:
  - Diltiazem or a pharmaceutically acceptable salt thereof as active principle,
  - a surfactant, and
  - a binder,
- and a layer which ensures sustained release of the active principle (SR layer).

2. Microgranules according to Claim 1, characterized in that the SR layer ensures slow sustained release of the active principle.

3. Microgranules according to Claim 1, characterized in that the SR layer ensures rapid sustained release of the active principle.

4. Microgranules according to Claim 2, characterized in that the SR layer which ensures slow sustained release of the active principle is itself coated with another active layer comprising:

- Diltiazem or a pharmaceutically acceptable salt thereof as active principle,
- a surfactant, and
- a binder,

itself coated with an external layer which ensures rapid sustained release of the active principle contained in this active layer.

5. Microgranules according to Claim 4, characterized in that they also comprise an intercalating layer between the SR layer which ensures slow release of the active principle and the active layer coating this SR layer.

6. Microgranules according to one of Claims 1 to 5, characterized in that the surfactant is an anionic, nonionic, cationic or amphoteric surfactant.

7. Microgranules according to Claim 6, characterized in that the surfactant is an anionic surfactant chosen, in particular, from alkali metal (C_{10}-C_{20})alkyl sulphates,

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preferably sodium lauryl sulphate, alkali metal (C_{10}-C_{20})alkyl sulphonates or alkali metal (C_{10}-C_{20})alkyl benzenesulphonates.

8. Microgranules according to one of Claims 1 to 7, characterized in that the binder consists of any pharmaceutically acceptable binder which is useful for coating neutral granular supports, in particular pharmaceutically acceptable polymers such as polyvinylpyrrolidones.

9. Microgranules according to one of Claims 1 to 8, characterized in that each active layer also comprises a plasticizer, preferably a phthalic acid ester.

10. Microgranules according to one of Claims 1 to 9, characterized in that the active principle/surfactant weight ratio is between 99/1 and 95/5, preferably about 98/2.

11. Microgranules according to one of Claims 1 to 10, characterized in that the active principle/binder weight ratio is between 99/1 and 90/10, preferably in the region of 97/3.

12. Microgranules according to one of Claims 1 to 3, characterized in that they comprise the following components for the support and the active layer, the percentages being given on a weight basis for a total of 100:

- neutral granular support	20 - 25%
- active principle	70 - 75%
- surfactant	0.5 - 5%
- binder	0.5 - 10%
- plasticizer	0 - 5%

13. Microgranules according to Claim 4, characterized in that they comprise the following components for the support and the active layers, the percentages being given on a weight basis for a total of 100:

- neutral granular support	10 - 20%
- active principle	75 - 85%
- surfactant	0.5 - 5%
- binder	0.5 - 10%
- plasticizer	0.5 - 5%

14. Microgranules according to one of Claims 1 to 13, characterized in that each SR layer consists of a coating

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agent which ensures sustained release, optionally combined with one or more common additives, in particular a bioavailability adjuvant and/or a plasticizer and/or a lubricant.

15. Microgranules according to Claim 14, characterized in that the coating agent ensuring the sustained release is a water-insoluble film-forming polymer, such as polymethacrylates.

16. Microgranules according to either of Claims 14 and 15, characterized in that the bioavailability adjuvant is preferably a fatty acid ester of polyoxyethylene, in particular those described under the name Polysorbate.

17. Microgranules according to one of Claims 14 to 16, characterized in that the lubricant is talc.

18. Microgranules according to one of Claims 14 to 17, characterized in that the plasticizer is a pharmaceutically acceptable common plasticizer used for the preparation of microgranules, in particular esters of citric, phthalic and sebacic acids, such as triethyl citrate, dibutyl sebacate or diethyl phthalate, and mixtures thereof.

19. Microgranules according to one of Claims 1 to 3, characterized in that they have the following final composition, the percentages being expressed on a dry weight basis for a total of 100%:

- neutral granular support	10 - 20%
• active layer:	
- active principle	45 - 65%
- binder	0.5 - 2%
- surfactant	0.5 - 1%
- plasticizer	0.5 - 1%
• SR layer:	
- coating agent	10 - 30%
- bioavailability adjuvant	0.05 - 0.15%
- plasticizer	2 - 10%
- lubricant	2 - 10%.

20. Microgranules according to Claim 4, characterized in that they have the following final composition, the

percentages being expressed on a dry weight basis for a total of 100%:

- neutral granular support	5 - 15%
• active layers:	
- active principle	45 - 65%
- binder	0.5 - 2.5%
- surfactant	0.75 - 1.25%
- plasticizer	0.75 - 1.25%
• SR layers:	
- coating agent	15 - 35%
- bioavailability adjuvant	0.02 - 0.15%
- plasticizer	2 - 10%
- lubricant	2 - 10%

21. Gelatin capsules comprising microgranules according to one of Claims 1 to 20.