Description

This invention relates to a controlled release pharmaceutical dosage form and a process for preparing same.

Various techniques for releasing drugs over an extended period of time have heretofore been known in the prior arts. For example, European Patent Publication No. 149920 discloses a controlled absorption pharmaceutical formulation comprising pellets having (i) a core of diltiazem in association with an organic acid and lubricant and (ii) an outer membrane which permits release of diltiazem in an aqueous medium. Further, a dosage form of pinacidil is prepared by the steps of coating a pinacidil-containing core with an enterosoluble polymer such as methacrylic acid-methylmethacryiate co-polymer, and then applying the layer containing pinacidil onto the surface of the core coated as above (Chemical Abstruct, 102, 172661 g (1985), Japanese Patent Publication (unexamined), No. 4120/1985).

An object of the present invention is to provide a controlled release dosage form which is able to control the release of a medicament, i.e., to obtain a therapeutically effective blood level of the medicament rapidly after the oral administration thereof and at the same time maintain such effective blood level over an extended period of time. Another object of the invention is to provide a process for preparation of the controlled dosage form by simpler procedures as compared with known methods.

Namely according to the present invention there is provided a controlled release pharmaceutical dosage form which comprises a water-soluble core containing diltiazem or diltiazem hydrochloride ; an inner coating layer composed of ethylcellulose and a hydrophobic substance selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight) ; and an outer coating layer containing diltiazem or diltiazem hydrochloride.

In making said controlled release dosage form, a pharmaceutically active compound or a mixture of a pharmaceutically active compound and excipients such as diluents, binders, lubricants or anti-aggregating agents can be used as the cores containing a medicament. The cores are preferably used in the form of granules or fine granules having a particle size of 300 μm-2000 μm, especially 500 μm-850 μm, in diameter. Although the hydrophobic cores have been used in some known methods for retarding the release of drugs from the dosage form, the cores of the invention are not necessarily hydrophobic and both of water-soluble and water-insoluble cores can be used in the present invention. Accordingly, a wide variety of excipients including diluents, binders, lubricants or anti-aggregating agents which are conventionally employed in this field can be used for preparing the cores of the present invention. Diluents which can be used in the present invention include, for example, saccharides such as sucrose, lactose or mannitol, starch, crystalline cellulose, calcium phosphate, calcium sulfate, calcium lactate and dextrose. Binders include, for example, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, polyvinylpyrrolidone, glucose, sucrose, lactose, maltose, sorbitol, mannitol, hydroxyethylcellulose, hydroxypropylmetylcellulose, hydroxypropylcellulose, macrogols, gum arabic, gelatin, agar and starch. Further, talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, waxes, hydrogenated oil, polyethylene glycols, sodium benzoate, sodium lauryl sulfate and magnesium lauryl sulfate are preferably used as lubricants or anti-aggregating agents.

The medicament-containing cores of the invention can be readily prepared in conventional manner. For example, said medicament-containing cores may be prepared by mixing a medicament with an appropriate excipient or excipients (i.e., diluents, binders, lubricants, etc.), and then granulating the mixture by the wet extrusing granulation, tumbling granulation or fluidized bed granulation method as described in Remington's pharmaceutical Sciences 17th Edition, pages 1603 to 1632 (Mark Publishing Company, 1985). Alternatively, the medicament-containing cores may be prepared according to the tumbling granulation, pan-coating or fluidized bed coating method as described in Remington's pharmaceutical Sciences 17th Edition, pages 1633 to 1643. For example, a solution of a binder in a solvent (e.g., water, a lower alkanol such as methanol, ethanol, propanol, isopropanol or butanol, a lower alkanone such as acetone or methylethylketone, chloroform, dichloromethane, dichloroethane or a mixture thereof) is sprayed on the surface of inert carrier particles, and during said spraying, the mixture of a medicament and an excipient or excipients such as diluents or lubricants is added gradually thereto, thereby the medicament-containing core being readily obtained. In the latter case, any particles of 300 μm to 1500 μm in diameter which are made of sucrose, lactose, starch, crystalline cellulose or other inert materials may be used as the inert carrier particles.

Among the components of the inner coating layer to be formed on the surface of the medicament-containing cores, ethylcellulose should preferably be water insoluble ethylcellulose and have an ethoxy content of about 40-55%, especially about 43-51% and a viscosity of about 0.004-0.35 Pa · s (4-350 cP) (measured in a 5 w/w% solution in toluene-ethanol (4 : 1) at 25°C).

On the other hand, a wide variety of materials which are insoluble in water and easily mixed with ethylcel-

lulose can be used as the hydrophobic substance. Example of the hydrophobic substance includes talc, alkali earth metal stearete such as magnesium stearate or calcium stearate, titaniun oxide, precipitated calcium carbonate, zinc oxide, colloidal silica and the like. Among them, talc and alkali earth metal stearate are preferred, especially talc is most preferred for use in the invention. These hydrophobic substances are preferably in the form of fine particles having a diameter of 0.1 μm-100 μm, especially 0.1 μm-20 μm. In preparing the inner coating layer, the quantitative ratio of ethylcellulose to the hydrophobic substance is preferably in the range of about 1 : 1 to about 1 : 15 (by weight), especially about 1 : 2 to 1 : 4 (by weight).

The inner coating layer can be formed on the surface of the medicament-containing cores in a conventional coating method such as, for example, the fluidized bed coating or pan-coating method as referred to above. The mixture of ethylcellulose and the hydrophobic substance to be sprayed on the medicament-containing cores may be used either in the form of a solution or a suspension. Water, a lower alkanol and a lower alkanone mentioned hereinbefore, chloroform dichloromethane, dichloroethane or a mixture thereof are suitable as a solvent for the coating solution or suspension. Said coating solution or suspension should preferably contain about 0.1-50%, especially 0.1-30% by weight, especially about 3-30%, more especialley 3-20% by weight, of the coating materials (i.e., ethylcellulose and the hydrophobic substance).

While the preferred coating ratio [(weight of ethylcellulose + hydrophobic substance/weight of the medicament-containing core) × 100] varies depending on the kind and content of medicaments, diluents, binders, lubricant or anti-aggregating agents to be incorporated in the core or desired release rate, said coating ratio is usually in the range of about 5-50%, especially about 5-40% and more especially about 10-30%.

In order to increase the accuracy for controlling the release rate of a medicament, a middle coating layer consisting of ethylcellulose alone or ethylcellulose and a water soluble substance may be, if desired, further coated on the surface of the inner coating layer prior to the coating of the outer coating layer. Suitable amount of ethylcellulose to be used as the middle coating layers is about 0.1-10%, especially about 1-5% by weight, of the amount of the core coated with the inner coating layer. Suitable examples of the water soluble substance which can be used for this purpose include sucrose, lactose, macrogols, mannitol and sorbitol. On the other hand, Ethylcellulose referred to above is preferably used for the middle coating layer. In case the water soluble substance is used together with ethylcellulose, preferred quantitative ratio of the water soluble substance to ethylcellulose is 1 : 1-20 : 1 (by weight). The coating of the middle coating layer can be carried out in the same manner as the coating of the inner coating layer, for example, by the fluidized bed coating or pan-coating methods referred to above. Namely, said middle coating layer may be readily obtained by spraying on the surface of the inner coating layer a solution of ethylcellulose or a solution of ethylcellulose and the water soluble substance in a solvent (e.g., a lower alkanol, water or a mixture thereof). Alternatively, when a mixture of ethylcellulose and the water soluble substance is employed as the middle coating layer, said coating may also be carried out by spraying simultaneously a solution of ethylcellulose and a solution of the water soluble substance.

A medicament alone, or its admixture with an appropriate excipient or excipients such as diluents, binders, lubricants and/or anti-aggregating agents can be used as the outer coating layer. Any diluents, binders, lubricants or anti-aggregating agents explained hereinbefore can be used. The amount of the medicament to be incorporated into the outer coating layer may be adjusted depending on the desired initial plasma level of the medicament. In general, however, suitable quantitative ratio of the medicament in the core to the medicament in the outer layer is in the range from about 1 : 1 to about 20 : 1 (by weight).

The outer coating layer can be prepared in a conventional manner, for example, by spraying a coating solution of the medicament or a coating solution containing the medicament and excipient(s) according to the fluidized bed coating or pan-coating method referred to hereinbefore. Alternatively, said coating may be carried out by spraying the solution of the medicament (or the solution containing the medicament and a lubricant and/or an anti-aggrigating agent) and the solution of a binder simultaneously. Water, a lower alkanol, a lower alkanone, chloroform dichloromethane, dichloroethane or a mixture thereof are preferably used as a solvent. The particle size of the controlled release dosage form which is prepared as granules in the present invention should preferably be in the range of about 500 μm-2500 μm, especially 700 μm-2000 μm, in diameter.

The thus-obtained dosage form of the invention may be, if desired, further coated with, for example, sucrose, lactose, magnesium stearate, waxes, talc or a mixture thereof in a conventional manner.

When the controlled release dosage form of the invention having the multi-layered structure is administered orally to a warm blooded aminal such as human beings, the medicament incorporated in the outer coating layers is rapidly released therefrom. On the other hand, the release and dissolution rate of the medicament incorporated in the cores is controlled because the inner coating layer surrounding the core retards the penetration or diffusion of the digestive-juce into the cores and the release of the medicament through the layer. Especially, the dosage form of the invention is characterized in that the hydrophobic substance used to form the uniform inner coating layer is embeded in ethylcellulose matrix and improves the impermeability of ethylcellulose to give wafer-permeability on the inner coating layer. Moreover, said structure of the inner coating layer remains intact

when the digestive-juice penetrates into the cores through the coating layers, and thus serves to release the medicament gradually at a constant rate. Accordingly, the dosage form of the invention, when administered, shows rapid increase in the blood concentration of the medicament and at the same time maintains the high level of the blood concentration of the medicament over a prolonged period of time because of the fast release of the medicament from the outer coating layer and also the controlled and sustained release of the medicament from the core medicaments or pharmaceutically active compounds to which the dosage form of the present invention can be applied include diltiazem hydrochloride and other diltiazem containing calcium-antagonists.

Further, the dosage form of the invention shows excellent bioavailability of the medicament and is quite effective to reduce the variation of blood level of the medicament i.e., to minimize the variation between the highest and lowest blood concentrations thereof. Therefore, even when the minimum therapeutically effective blood level of a medicament is close to the toxic blood level thereof, the dosage form of the invention can be used to exert the therapeutic effect of such medicament while keeping the blood level thereof lower than the toxic level.

Besides, according to the present invention, a controlled release dosage form having uniformity in the content of the medicament can easily be prepared in simple manner by using a conventional apparatus. Furthermore, the dosage form of the invention is also advantageous in that the release rate of the medicament from the core can easily be controlled by changing the quantitative ratio of ethylcellulose to the hydrophobic substance to be used for the inner coating layers or changing the coating ratio of the inner coating layers.

The invention also includes in one of its aspects a process for preparing a controlled release dosage form comprising the steps of :

(1) coating a water-soluble core containing diltiazem or diltiazem hydrochloride with an inner coating layer composed of ethylcellulose and a hydrophobic substance (wherein said hydrophobic substance is selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, and the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight)), and

(2) coating the product of step (1) with an outer coating layer containing diltiazem or diltiazem hydrochloride.

Example 1 (granules)

(1) The medicament-containing core

(Ingredients)	(weight %)
Inert carrier particle	17.5
Diltiazem hydrochloride	69.7
Polyvinylpyrrolidone	7.0
Talc	5.8
Total	100.0

800 g of the inert carrier particle (sucrose seeds of 710 to 840 µm (20 to 24 meshes), Trade name : Nonpareil manufactured by Freund Industry Co.) are tumbled in the centrifugal fluidizing granulator (Freund Industry Co., hereinafter, referred to as CF granulator). A mixture of 3200 g of diltiazem hydrochloride and 267 g of talc is spreaded onto the inert carrier particle gradually while spraying 3520 g of a polyvinylpyrrolidone-80% ethanol solution (polyvinylpyrrolidone content : 320g) at a rate of 15 ml/min..

The products thus obtained are air-dried at 50°C and then sieved, whereby about 4400 g of the medicament-containing core having the particle size of 1410 to 1680 µm (10 to 20 meshes) are obtained.

(2) Inner coating layer

(Ingredients)	(weight %)
Medicament-containing core obtained in paragraph (1)	87.0
Ethylcellulose	2.6
Talc	10.4
Total	100.0

4388 g of the medicament-containing core obtained in paragraph (1) are tumbled in the CF granulator. A solution of 133.2 g of ethylcellulose [ethoxy content : 48-49.5%, viscosity (measured at 25°C with respect to a toluene-ethanol (4 : 1) solution : 0.009-0.011 Pa · s (9-11 cP)] and 525.6 g of talc in 2530 g of 80% ethanol is sprayed onto the cores at a rate of about 30 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5000 g of grandules having the particle size of 1410 to 1680 µm (10 to 20 meshes) are obtained.

(3) Middle coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (2)	87.4
Ethylcellulose	1.5
Sucrose	11.1
Total	100.0

4907 g of granules obtained in paragraph (2) are tumbled in the Cf granulator. A solution of 77 g of ethylcellulose [the ethoxy content and viscosity are the same as defined in paragraph (2)] and 626.5 g of sucrose in 1463 g of 60% ethanol is sprayed onto the granules at a rate of about 30 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5500 g of granules having the particle size of 1410 to 1680 µm (10 to 20 meshes) are obtained.

(4) Outer coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (3)	91.5
Diltiazem hydrochloride	8.5
Total	100.0

5450.2 g of granules obtained in paragraph (3) are tumbled in the Cf granulator. A solution of 510 g of diltiazem hydrochloride in 2040 g of 60% ethanol is sprayed onto the granules at a rate of about 20 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5850 g of granules having the particle size of 1410 to 1680 µm (10 to 20 meshes) are obtained.

(5) Surface coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (4)	92.3
Sucrose	7.1
Talc	0.6
Total	100.0

5837.5 g of granules obtained in paragraph (4) are tumbled in the Cf granulator. A suspension of 450 g of sucrose and 40 g of talc in 460 g of 25% ethanol is sprayed onto the granules at a rate of about 25 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 6200 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Example 2 (granules)

(1) Middle coating layer

(Ingredients)	(weight %)
Granules obtained in Example 1-(2)	98.3
Ethylcellulose	1.7
Total	100.0

A solution of 84 g of ethylcellulose [the ethoxy content and viscosity are the same as defined in Example 1-(2)] in 1600 g of 80% ethanol is applied to 4907 g of granules obtained in Example 1-(2) in the same manner as described in Example 1-(3), whereby about 4900 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(2) Outer coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (1)	89.8
Ethylcellulose	0.7
Diltiazem hydrochloride	9.5
Total	100.0

4891.2 g of granules obtained in paragraph (1) are tumbled in the CF granulator. A solution of 514.5 g of diltiazem hydrochloride and 41.2 g of ethylcellulose [the ethoxy content and viscosity are the same as defined in Example 1-(2)] in 3080 g of 70% ethanol is sprayed onto the granules at a rate of about 25 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5300 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(3) Surface coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (2)	83.6
Sucrose	13.8
Talc	2.6
Total	100.0

875.8 g of sucrose, 880 g of 25% ethanol and 163.2 g of talc are applied to 5288 g of granules obtained in paragraph (2) in the same manner as described in Example 1-(5), whereby about 6200 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Example 3 (granules)

Outer coating layer

(Ingredients)	(weight %)
Granules obtained in Example 2-(1)	87.7
Diltiazem hydrochloride	6.1
Sucrose	6.2
Total	100.0

4980 g of granules obtained in Example 2-(1) are tumbled in the CF granulator. 349 g of diltiazem hydrochloride is added gradually while a solution of 349 g of sucrose in 25% ethanol is sprayed onto the granules at a rate of about 20 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5450 g of granules having the particle size of 1410 to 1680 μm of (10 to 20 meshes) are obtained.

Example 4 (granules)

(1) Inner coating layer

(Ingredients)	(weight %)
Medicament-containing core obtained in Example 1-(1)	77.0
Ethylcellulose	11.5
Talc	11.5
Total	100.0

658.8 g of ethylcellulose [the ethoxy content and viscosity are the same as defined in Example 1-(2)], 658.8 g of talc and 6000 g of 80% ethanol are applied to 4388 g of the medicament-containing core obtained in Example 1-(1) in the same manner as described in Example 1-(2), whereby about 5600 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(2) Outer coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (1)	94.1
Diltiazem hydrochloride	5.9
Total	100.0

5547 g of granules obtained in paragraph (1) are tumbled in the CF granulator. A solution of 350 g of diltiazem hydrochloride in 1400 g of 25% ethanol is sprayed onto the granules at a rate of about 30 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 5780 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(3) Surface coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (2)	92.1
Sucrose	7.4
Talc	0.5
Total	100.0

459 g of sucrose, 34 g of talc and 60 g of 25% ethanol are applied to 5712 g of granules obtained in paragraph (2) in the same manner as described in Example 1-(5), whereby about 6000 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Examples 5 to 7 (granules)

The inner coating layer, outer coating layer and surface coating layer are successively formed on 4388 g of the medicament-containing cores obtained in Example 1-(1) in the same manner as described in Example 4 except that the ingredients shown in following Table 1 are used for the inner coating layer. About 6000 g of granules having the particle size of 1410 to 1680 μm of (10 to 20 meshes) are obtained, respectively.

Table 1

	Ingredients of the inner coating layer (weight %)			
Example Nos.	Medicament-containing core obtained in Example 1-(1)	Ethyl-cellulose*	Talc	Total
5	77.0	7.6	15.4	100.0
6	77.0	4.6	18.4	100.0
7	77.0	1.4	21.6	100.0

*: The ethoxy content and viscosity are the same as defined in Example 1-(2)

Examples 8 to 11 (granules)

(1) Inner coating layer

The inner coating layer is applied to 4388 g of the medicament-containing cores obtained in Example 1-(1) in the same manner as described in Example 1-(2) except that the ingredients shown in following Table 2 are used for the inner coating layer. Granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Table 2

	Ingredients of the inner coating layer (weight %)			
Example Nos.	Medicament-containing core obtained in Example 1-(1)	Ethyl-cellulose*	Talc	Total
8-(1)	90.9	1.5	7.6	100.0
9-(1)	83.3	2.8	13.6	100.0
10-(1)	76.9	3.9	19.2	100.0
11-(1)	71.4	4.8	23.8	100.0

*: The ethoxy content and viscosity are the same as defined in Example 1-(2)

(2) Outer coating layer

Granules obtained in paragraph (1) and diltiazem hydrochloride are treated in the same manner as described in Example 4-(2) except that the ingredients shown in table 3 are used for the outer coating layer. Granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained. The yields of the granules are shown in Table 3.

Table 3

	Ingredients (weight %)			Yields of the granules (Grams)
Example Nos.	Granules obtained in the paragraph(1)	Diltiazem hydrochloride	Total	
8-(2)	93.1	6.9	100.0	ca. 4900
9-(2)	93.6	6.4	100.0	ca. 5200
10-(2)	94.1	5.9	100.0	ca. 5750
11-(2)	94.5	5.5	100.0	ca. 6200

Examples 12 to 13 (granules)

(1) Inner coating layer

The inner coating layer is applied to 4388 g of the medicament-containing cores obtained in Example 1-(1) in the same manner as described in Example 1-(2) except that magnesium stearate in an amount shown in the following Table 4 is used instead of talc.

Table 4

	Ingredients of the inner coating layer (weight %)			
Example Nos.	Medicament-containing core obtained in Example 1-(1)	Ethyl-cellulose*	Magnesium stearate	Total
12-(1)	90.9	1.9	7.2	100.0
13-(1)	83.3	3.4	13.3	100.0

*: The ethoxy content and viscosity are the same as defined in Example 1-(2)

(2) Outer coating layer

Granules obtained in paragraph (1) and diltiazem hydrochloride are treated in the same manner as described in Example 4-(2). Granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained. The amount of ingredient used and the yields of the granules are shown in Table 5.

Table 5

	Ingredients (weight %)			Yields of the granules (Grams)
Example Nos.	Granules obtained in the paragraph(1)	Diltiazem hydrochloride	Total	
12-(2)	93.6	6.4	100.0	ca. 5200
13-(2)	94.1	5.9	100.0	ca. 5700

Example 14 (capsules)

Granules obtained in Example 1 are filled in hard capsules No. 3 to give the capsules containing 100 mg of diltiazem hydrochloride in each capsule.

Example 15 (capsules)

Granules obtained in Example 2 are filled in hard capsules No. 3 to give the capsules containing 100 mg of diltiazem hydrochloride in each capsule.

Example 16 (granules)

(1) Medicament-containing core

(Ingredients)	(weight %)
Inert carrier particle	28.0
Theophylline	56.0
Sucrose	16.0
Total	100.0

1400 g of the inert carrier particle (sucrose seeds of 710 to 840 μm (20 to 40 meshes), Trade name : Nonpareil, manufactured by Freund Industry Co.) are tumbled in the CF granulator. 2800 g of theophylline are spreaded thereto gradually while spraying 3200 ml of a 25% aqueous sucrose solution onto the seeds at a rate of 15 ml/min. The products thus obtained are air-dried at 50°C and then sieved, whereby about 4400 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(2) Inner coating layer

(Ingredients)	(weight %)
Medicament-containing core obtained in paragraph (1)	84.4
Ethylcellulose	2.6
Talc	13.0
Total	100.0

4220 g of the medicament-containing core obtained in paragraph (1) are tumbled in the CF granulator. A solution of 130.0 g of ethylcellulose [the ethoxy content and viscosity are the same as defined in Example 1-(2)] and 650.0 g of talc in 2530 g of 80% ethanol is sprayed onto the granules at a rate of about 30 ml/min. After the coating, the products are air-dried at 50°C and then sieved, whereby about 4950 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(3) Outer coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (2)	74.0
Theophylline	17.5
Sucrose	8.5
Total	100.0

4800 g of the granules obtained in paragraph (2) are tumbled in the CF granulator. 1135 g of theophylline are spreaded thereto gradually while spraying 920 ml of a 60% aqueous sucrose solution onto the granules at a rate of about 20 ml/min. The products thus obtained are air-dried at 50°C and then sieved, whereby about 6400 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Example 17 (granules)

(1) Inner coating layer

(Ingredients)	(weight %)
Medicament-containing core obtained in Example 16-(1)	84.4
Ethylcellulose	1.7
Talc	13.9
Total	100.0

4220 g of the medicament-containing core obtained in Example 16-(1), 85.0 g of ethylcellulose, 695.0 g of talc and 600 g of 80% ethanol are treated in the same manner as described in Example 16-(2), whereby about 4900 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

(2) Outer coating layer

(Ingredients)	(weight %)
Granules obtained in paragraph (1)	74.0
Theophylline	17.5
Sucrose	8.5
Total	100.0

4800 g of granules obtained in paragraph (1) and 1135 g of theophylline are treated in the same manner as described in Example 16-(3), whereby about 6400 g of granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Examples 18 to 22 (granules)

The inner coating layer, outer coating layer and surface coating layer are successively formed on the medicament-containing cores obtained in Example 1-(1) in the same manner as described in Example 1-(2)-(5) except that a hydriphybic substance shown in Table 6 is used for the inner coating layer instead of talc.

Granules having the particle size of 1410 to 1680 μm (10 to 20 meshes) are obtained.

Table 6

Example Nos.	The hydrophobic substance used for the inner coating layer
18	calcium stearate
19	titanium oxide
20	precipitated calcium carbonate
21	zinc oxide
22	colloidal silica

Examples 23 to 26 (granules)

The inner coating layer, outer coating layer and surface coating layer are successinely formed on the medicament-containing cores obtained in Example 1-(1) in the same manner as described in Example 1-(2)-(5) except that a water soluble material shown in Table 7 is used for the middle coating layer inslead of sucrose. Granules having thje particle size of 1410 to 1680 µm (10 to 20 meshes) are obtained.

Table 7

Example Nos.	Water soluble substance used for the middle layer
23	lactose
24	macrogol 6000
25	mannitol
26	sorbitol

Experiment 1 (dissolution test)

The effect of the quantitative ratio of ethylcellulose and a hydrophobic substance in the inner coating layer on the dissolution rate of the medicament is investigated by using the granules of Examples 4 to 7.

[Sample used]

1 : Granules obtained in Example 4-(3)
2 : Granules obtained in Example 5
3 : Granules obtained in Example 6
4 : Granules obtained in Example 7

[Test method]

Dissolution test was performed according to the second dissolution test method (Paddle Method) specified in THE PHARMACOPOEIA OF JAPAN 10th-edition by adding each sample of the granules (dose of diltiazem hydrochloride : 100 mg) to 900 ml of distilled water under stirring at 100 rpm at 37°C. 10 ml of the solution was collected at intervals and the dissolution percentage of the medicament (diltiazem hydrochloride) was calculated based on the absorbance of the sample solution measured at 285 nm.

[Results]

The results are shown in Fig. 1. The curves A, B, C and D in Fig. 1 show time-course changes in the dissolution percentages of the medicament (diltiazem hydrochloride) from the granules of Examples 4, 5, 6 and 7, respectively. From these results, it is demonstrated that various dissolution patterns of the medicament are available by adjusting the quantitative ratio of ethylcellulose and talc in a range of 1 : 1 to 1 : 15.

Experiment 2 (dissolution test)

The effect of the coating amount of the inner coating layer on the dissolution rate of the medicament is investigated according to the test method described in Experiment 1 by using the granules of Examples 8 to 11.

[Samples]

1 : Granules obtained in Example 8
2 : Granules obtained in Example 9
3 : Granules obtained in Example 10
4 : Granules obtained in Example 11

[Results]

The results are shown in Fig. 2. The curves E, F, G and H in Fig. 2 show time-course changes in the dissolution percentage of the medicament from the granules of Examples 8, 9, 10 and 11, respectively. From these results, it is shown that the dissolution patterns of the medicament can be also controlled by adjusting the coating amounts of the inner coating layer.

Experiment 3 (dissolution test)

The dissolution percentages of the medicament from the dosage form of the present invention are investigated according to the test method described in Experiment 1 by using the capsules obtained in Examples 14 and 15.

[Results]

The results are shown in Fig. 3. The curves I and J in Fig. 3 show the time-course changes in the dissolution percentage of the medicament from the capsules of Examples 14 and 15, respectively. From these results, it is clear that the dissolution rate of the dosage form of the present invention is well controlled over a prolonged period of time.

Experiment 4 (dissolution test)

The dissolution tests of the granules obtained in Example 12, 13, 16 and 17 are performed in accordance with the test method described in Experiment 1. In this experiment, the dissolution rate of theophylline is determined based on the absorbance of the sample solution measured at 292 nm.

[Results]

The dissolution percentages of the medicament (theophylline) are shown in Table 8.

Table 8

Samples	Percentage of dissolution (%)							
	Time (hr)							
	0.5	1	3	5	7	10	14	20
Granules in Exp. 12	11	12	18	26	40	65	89	100
Granules in Exp. 13	10	11	14	18	20	26	39	66
Granules in Exp. 16	35	37	43	49	55	68	80	92
Granules in Exp. 17	40	46	67	85	95	100	100	100

Experiment 5 (measurement of prasma level)

One capsule obtained in Example 15 (dose of the diltiazem hydrochloride : 100 mg) is orally administered together with 100 ml of water to healthy volunteers (adult male, body weight : 55 to 68 kg). Blood samples are collected at intervals from the vein of forearms, and then plasma samples were obtained therefrom by centrifugation. The concentrations of the medicament (diltiazem hydrochloride) in plasma are determined by using high performance liquid chromatography.

[Results]

The results are shown in Fig. 4. In this figure, the curve shows the plasma levels of the medicament (diltiazem hydrochloride). From these results it is demonstrated that the dosage form of the present invention shows a prolonged plasma profile of the medicament with a suitable initial plasma level thereof.

[Brief Description of Drawings]

Figures 1, 2 and 3 show graphs of dissolution percentage versus time of granules (or capsules) of Examples 4 to 7, Examples 8 to 11, and Examples 14 to 15, respectively.

Figure 4 shows graphs of plasma levels versus time after oral administration of capsule of Example 15.

Claims

Claims for the following Contracting States : DE, GB, IT, NL, SE, CH, LI, BE, LU

1. A controlled release pharmaceutical dosage form which comprises a water-soluble core containing diltiazem or diltiazem hydrochloride ; an inner coating layer composed of ethylcellulose and a hydrophobic substance selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight) ; and an outer coating layer containing diltiazem or diltiazem hydrochloride.

2. The controlled release dosage form claimed in claim 1, in which a middle coating layer composed of ethylcellulose alone or a mixture of ethylcellulose and a water-soluble substance selected from sucrose, lactose, macrogol, mannitol and sorbitol, the quantitative ratio of said water-soluble substance to ethylcellulose being in the range of 1 : 1 to 20 : 1 (by weight), is further formed between the inner coating layer and the outer coating layer.

3. The controlled release dosage form claimed in claim 1 or claim 2, in which the quantitative ratio of the diltiazem or diltiazem hydrochlorid incorporated in the core to the diltiazem or diltiazem hydrochloride incorported in the outer coating layer is within a range of 1 : 1 to 20 ; 1 (by weight).

4. The controlled dosage form claimed in any preceding claim, in which the particle size of the core containing the diltiazem or diltiazem hydrochloride is in the range of 300 μm to 2000 μm in diameter, the coating ratio [(weight of ethylcellulose + hydrophobic substance/weight of the medicament-containing core) × 100] of the inner coating layer is in the range of 5-50%, and the amount of ethylcellulose to be used in the middle coating layer is in the range of 0.1 to 10% of the amount of the inner coating layer-coated core.

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Table 8

Samples	Percentage of dissolution (%)							
	Time (hr)							
	0.5	1	3	5	7	10	14	20
Granules in Exp. 12	11	12	18	26	40	65	89	100
Granules in Exp. 13	10	11	14	18	20	26	39	66
Granules in Exp. 16	35	37	43	49	55	68	80	92
Granules in Exp. 17	40	46	67	85	95	100	100	100

Experiment 5 (measurement of prasma level)

One capsule obtained in Example 15 (dose of the diltiazem hydrochloride : 100 mg) is orally administered together with 100 ml of water to healthy volunteers (adult male, body weight : 55 to 68 kg). Blood samples are collected at intervals from the vein of forearms, and then plasma samples were obtained therefrom by centrifugation. The concentrations of the medicament (diltiazem hydrochloride) in plasma are determined by using high performance liquid chromatography.

[Results]

The results are shown in Fig. 4. In this figure, the curve shows the plasma levels of the medicament (diltiazem hydrochloride). From these results it is demonstrated that the dosage form of the present invention shows a prolonged plasma profile of the medicament with a suitable initial plasma level thereof.

[Brief Description of Drawings]

Figures 1, 2 and 3 show graphs of dissolution percentage versus time of granules (or capsules) of Examples 4 to 7, Examples 8 to 11, and Examples 14 to 15, respectively.

Figure 4 shows graphs of plasma levels versus time after oral administration of capsule of Example 15.

Claims

Claims for the following Contracting States : DE, GB, IT, NL, SE, CH, LI, BE, LU

1. A controlled release pharmaceutical dosage form which comprises a water-soluble core containing diltiazem or diltiazem hydrochloride ; an inner coating layer composed of ethylcellulose and a hydrophobic substance selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight) ; and an outer coating layer containing diltiazem or diltiazem hydrochloride.

2. The controlled release dosage form claimed in claim 1, in which a middle coating layer composed of ethylcellulose alone or a mixture of ethylcellulose and a water-soluble substance selected from sucrose, lactose, macrogol, mannitol and sorbitol, the quantitative ratio of said water-soluble substance to ethylcellulose being in the range of 1 : 1 to 20 : 1 (by weight), is further formed between the inner coating layer and the outer coating layer.

3. The controlled release dosage form claimed in claim 1 or claim 2, in which the quantitative ratio of the diltiazem or diltiazem hydrochlorid incorporated in the core to the diltiazem or diltiazem hydrochloride incorported in the outer coating layer is within a range of 1 : 1 to 20 ; 1 (by weight).

4. The controlled dosage form claimed in any preceding claim, in which the particle size of the core containing the diltiazem or diltiazem hydrochloride is in the range of 300 μm to 2000 μm in diameter, the coating ratio [(weight of ethylcellulose + hydrophobic substance/weight of the medicament-containing core) × 100] of the inner coating layer is in the range of 5-50%, and the amount of ethylcellulose to be used in the middle coating layer is in the range of 0.1 to 10% of the amount of the inner coating layer-coated core.

5. The controlled release dosage form claimed in claim 4, in which said dosage form is granules having a particle size of 500 μm to 2500 μm in diameter.

6. The controlled release dosage form claimed in any one of the preceding claims in which the hydrophobic substance is talc, magnesium stearate, calcium stearate, titanium, oxide, precipitated calcium carbonate, zinc oxide or colloidal silica.

7. The controlled release dosage form claimed in any one of the preceding claims wherein the diltiazem is in the form of the hydrochloride salt.

8. A process for preparing a controlled release dosage form comprising the steps of :

(1) coating a water-soluble core containing diltiazem or diltiazem hydrochloride with an inner coating layer composed of ethylcellulose and a hydrophobic substance (wherein said hydrophobic substance is selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, and the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight)), and

(2) coating the product of step (1) with an outer coating layer containing diltiazem or diltiazem hydrochloride.

9. A process as claimed in claim 8 including further the step of coating the granules of step (1) with a middle coating layer composed of ethylcellulose alone or a mixture of ethylcellulose and a water-soluble substance selected from sucrose, lactose, macrogol, mannitol and sorbitol, and a quantitative ratio of said water-soluble substance to ethylcellulose being in the range of 1 : 1 to 20 : 1 (by weight), prior to the coating of the outer coating layer.

10. A process as claimed in claim 8 or claim 9 wherein the diltiazem is in the form of the hydrochloride salt.

Claims for the following Contracting States : ES, GR

1. A process for preparing a controlled release dosage form comprising the steps of :

(1) coating a water-soluble core containing diltiazem or diltiazem hydrochloride with an inner coating layer composed of ethylcellulose and a hydrophobic substance (wherein said hydrophobic substance is selected from talc, alkali earth metal stearate, titanium oxide, precipitated calcium carbonate, zinc oxide and colloidal silica, and the quantitative ratio of ethylcellulose to said hydrophobic substance being within a range of 1 : 1 to 1 : 15 (by weight)), and

(2) coating the product of step (1) with an outer coating layer containing diltiazem or diltiazem hydrochloride.

2. A process as claimed in claim 1 including further the step of coating the granules of step (1) with a middle coating layer composed of ethylcellulose alone or a mixture of ethylcellulose and a water-soluble substance selected from sucrose, lactose, macrogol, mannitol and sorbitol, and a quantitative ratio of said water-soluble substance to ethylcellulose being in the range of 1 : 1 to 20 : 1 (by weight), prior to the coating of the outer coating layer.

3. A process as claimed in claim 1 or claim 2, in which the quantitative ratio of the diltiazem or diltiazem hydrochloride incorporated in the core to the diltiazem or diltiazem hydrochloride incorporated in the outer coating layer is within a range of 1 : 1 to 20 : 1 (by weight).

4. A process as claimed in claim 3, in which the particle size of the core containing diltiazem or diltiazem hydrochloride is in the range of 300 μm to 2000 μm in diameter, the coating ratio [(weight of ethylcellulose + hydrophobic substance/weight of the medicament-containing core) × 100] of the inner coating layer is in the range of 5-50%, and the amount of ethylcellulose to be used in the middle coating layer is in the range of 0.1 to 10% of the amount of the inner coating layer-coated core.

5. A process as claimed in claim 4, in which said dosage form is granules having a particle size of 500 μm to 2500 μm in diameter.

6. A process as claimed in any one of the preceding claims in which the hydrophobic substance is talc, magnesium stearate, calcium stearate, titanium, oxide, precipitated calcium carbonate, zinc oxide or colloidal silica.

7. A process as claimed in any one of the preceding claims wherein the diltiazem is in the form of the hydrochloride salt.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, IT, NL, SE, CH, LI, BE, LU

1. Forme de dosage pharmaceutique à libération controlée comprenant un noyau soluble dans l'eau contenant du diltiazem ou de l'hydrochlorure de diltiazem ; une couche intérieure de revêtement composée d'éthylcellulose et d'une substance hydrophobe choisie parmi le talc, le stearate de métaux alcalino-terreux, l'oxyde de titanium, le carbonate de calcium précipité, l'oxyde de zinc et le dioxyde de silicium colloïdal, le rapport quantitatif entre l'éthylcellulose et la dite substance hydrophobe étant de l'ordre de 1 : 1 à 1 : 15 (en poids) ; et une couche de revêtement extérieure contenant du diltiazem ou de l'hydrochlorure de diltiazem.

2. Forme de dosage à libération contrôlée selon la revendication 1, dans laquelle une couche de revêtement intermédiaire, composée uniquement d'éthylcellulose ou d'un mélange d'éthylcellulose et d'une substance soluble dans l'eau choisie parmi la sucrose, la lactose, le macrogol, le mannitol et le sorbitol, le rapport quantitatif entre la dite substance soluble dans l'eau et l'éthylcellulose étant de l'ordre de 1 : 1 à 20 : 1 (en poids), est de plus formée entre la couche de revêtement intérieure et la couche de revêtement extérieure.

3. Forme de dosage à libération contrôlée selon la revendication 1 ou la revendication 2, dans laquelle le rapport quantitatif entre le diltiazem ou l'hydrochlorure de diltiazem incorporé dans le noyau et le diltiazem ou l'hydrochlorure de diltiazem incorporé dans la couche extérieure de revêtement est de l'ordre de 1 : 2 à 20 : 1 (en poids).

4. Forme de dosage à libération contrôlée selon l'une quelconque des revendications qui précèdent, dans laquelle la grandeur des particules du noyau contenant le diltiazem ou l'hydrochlorure de diltiazem est de l'ordre de 300 µ à 2000 µm en diamètre, la proportion de revêtement [(poids de l'éthylcellulose + substance hydrophobe/poids du noyau contenant le médicament) x 100] de la couche de revêtement intérieure est de l'ordre de 5-50%, et la quantité d'éthylcellulose à utiliser dans la couche intermédiaire de revêtement est de l'ordre de 0,1 à 10% de la proportion de noyau revêtue par la couche de revêtement intérieure.

5. Forme de dosage à libération contrôlée selon la revendication 4, dans laquelle la forme de dosage est constituée de granules dont la dimension des particules est de 500 µm à 2500 µm de diamètre.

6. Forme de dosage à libération contrôlée selon l'une quelconque des revendications précédentes dans laquelle la substance hydrophobe est le talc, le stéarate de magnésium, le stéarate de calcium, l'oxyde de titanium, le carbonate de calcium précipité, l'oxyde de zinc ou le dioxyde de silicium colloïdal.

7. Forme de dosage à libération contrôlée selon l'une quelconque des revendications précédentes dans laquelle le diltiazem se trouve sous la forme de sel hydrochlorure.

8. Procédé de préparation d'une forme de dosage à libération contrôlée comprenant les étapes consistant à :

(1) revêtir un noyau soluble dans l'eau, contenant du diltiazem ou de l'hydochlorure de diltiazem, d'une couche de revêtement intérieure composée d'éthylcellulose et d'une substance hydrophobe (la dite substance étant choisie parmi le talc, le stéarate de métaux alcalino-terreux, l'oxyde de titanium, le carbonate de calcium précipité, l'oxyde de zinc et le dioxyde de silicium colloïdal), et le rapport quantitatif entre l'éthylcellulose et la dite substance hydrophobe étant de l'ordre de 1 : 1 à 1 : 15 (en poids), et

(2) revêtir le produit de l'étape (1) d'une couche de revêtement extérieure contenant du diltiazem ou de l'hydrochlorure de diltiazem.

9. Procédé selon la revendication 8 incluant de plus l'étape constituant à revêtir les granules selon l'étape (1) d'une couche de revêtement intermédiaire composée d'éthylcellulose uniquement ou d'un mélange d'éthylcellulose et d'une substance soluble dans l'eau choisie parmi la sucrose, la lactose, le macrogol, le mannitol et le sorbitol, et le rapport quantitatif entre la dite substance soluble dans l'eau et l'éthylcellulose étant de l'ordre de 1 : 1 à 20 : 1 (en poids), avant d'appliquer la couche extérieure de revêtement.

10. Procédé selon la revendication 8 ou la revendication 9 dans lequel le diltiazem est sous forme de sel hydrochlorure.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour préparer une forme de dosage à libération contrôlée comprenant les étapes consistant à :

(1) revêtir un noyau soluble dans l'eau contenant du diltiazem ou de l'hydrochlorure de diltiazem d'une couche de revêtement intérieure composée d'éthylcellulose et d'une substance hydrophobe (la dite substance hydrophobe étant sélectionnée parmi le talc, le stéarate de métaux alcalino-terreux, l'oxyde de titanium, le carbonate de calcium précipité, l'oxyde de zinc et le dioxyde de silicium colloïdal), et le rapport quantitatif entre l'éthylcellulose et la dite substance hydrophobe étant de l'ordre de 1 : 1 à 1 : 15 (en poids), et

(2) revêtir le produit de l'étape (1) avec une couche de revêtement extérieure contenant du diltiazem ou de l'hydrochlorure de diltiazem.

2. Procédé selon la revendication 1 comprenant de plus l'étape consistant à revêtir les granules de l'étape (1) d'une couche de revêtement intermédiaire composée d'éthylcellulose uniquement ou d'un mélange d'éthylcellulose et d'une substance soluble dans l'eau choisie parmi la sucrose, la lactose, le macrogol, le mannitol et sorbitol, et le rapport quantitatif entre la dite substance soluble dans l'eau et l'éthylcellulose étant de l'ordre de 1 : 1 à 20 : 1 (en poids), avant d'appliquer la couche de revêtement extérieure.

3. Procédé selon la revendication 1 ou la revendication 2, dans laquelle le rapport quantitatif entre le diltiazem ou l'hydrochlorure de diltiazem incorporé dans le noyau et le diltiazem ou l'hydrochlorure de diltiazem incorporé dans la couche de revêtement extérieure est de l'ordre de 1 : 1 à 20 : 1 (en poids).

4. Procédé selon la revendication 3, dans lequel les dimensions des particules du noyau contenant le diltiazem ou l'hydrochlorure de diltiazem est de l'ordre de 300 µm a 2000 µm en diamètre, la proportion de revêtement [(poids de l'éthylcellulose + substance hydrophobe/poids du noyau contenant le médicament) × 100] de la couche intérieure de revêtement est de l'ordre de 5-50%, et la quantité d'éthylcellulose à utiliser pour la couche intermédiaire de revêtement est de l'ordre de 0,1 à 10% de la quantité de noyau revêtue de la couche de revêtement intérieure.

5. Procédé selon la revendication 4, dans lequel la dite forme de dosage est faite de granules dont la dimension des particules est de 500 µm à 2500 µm en diamètre.

6. Procédé selon l'une quelconque des revendications précédentes dans lequel la substance hydrophobe est du talc, du stéarate de magnésium, du stéarate de calcium, de l'oxyde de titanium, du carbonate de calcium précipité, de l'oxyde de zinc ou du dioxyde de silicium colloïdal.

7. Procédé selon l'une quelconque des revendications précédentes dans lequel le diltiazem se trouve sous forme de sel hydrochlorure.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, DE, GB, IT, NL, SE, CH, LI, BE, LU

1. Pharmazeutische Dosisform mit gesteuerter Freisetzung, welche einen Diltiazem oder Diltiazemhydrochlorid enthaltenden wasserlöslichen Kern, eine innere Überzugsschicht bestehend aus Äthylcellulose und einer hydrophoben Substanz ausgewählt aus Talkum, Erdalkalimetallstearat, Titanoxid, ausgefälltem Calciumcarbonat, Zinkoxid und kolloidalem Siliziumdioxid, wobei das Mengenverhältnis von Äthylcellulose zur hydrophoben Substanz in einem Bereich von 1 : 1 bis 1 : 15 (bezogen auf das Gewicht) liegt, und eine Diltiazem oder Diltiazemhydrochlorid enthaltende äußere Überzugsschicht umfaßt.

2. Dosisform mit gesteuerter Freisetzung nach Anspruch 1, in welcher eine mittlere Überzugsschicht bestehend aus Äthylcellulose alleine oder aus einer Mischung aus Äthylcellulose und einer wasserlöslichen Substanz ausgewählt aus Saccharose, Lactose, Macrogol, Mannit und Sorbit, wobei das Mengenverhältnis der wasserlöslichen Substanz zu Äthylcellulose im Bereich von 1 : 1 bis 20 : 1 (bezogen auf das Gewicht) liegt, weiters zwischen der inneren Überzugsschicht und der äußeren Überzugsschicht gebildet ist.

3. Dosisform mit gesteuerter Freisetzung nach Anspruch 1 oder Anspruch 2, in welcher das Mengenverhältnis von im Kern enthaltenem Diltiazem oder Diltiazemhydrochlorid zum in der äußeren Überzugsschicht enthaltenen Diltiazem oder Diltiazemhydrochlorid in einem Bereich von 1 : 1 bis 20 : 1 (bezogen auf das Gewicht) liegt.

4. Dosisform mit gesteuerter Freisetzung nach irgendeinem vorhergehenden Anspruch, worin die Teilchengröße des das Diltiazem oder Diltiazemhydrochlorid enthaltenden Kerns im Bereich von 300 µm bis 2000 µm im Durchmesser beträgt, wobei das Beschichtungsverhältnis [(Gewicht von Äthylcellulose + hydrophober Substanz/Gewicht des medikamenthältigen Kerns) × 100] der inneren Überzugsschicht im Bereich von 5-50% und die Menge der in der mittleren Überzugsschicht zu verwendenden Äthylcellulose im Bereich von 0,1 bis 10% der Menge des mit einer inneren Überzugsschicht überzogenen Kerns liegt.

5. Dosisform mit gesteuerter Freisetzung nach Anspruch 4, worin die Dosisform Granula mit einer Teilchengröße von 500 µm bis 2500 µm im Durchmesser ist.

6. Dosisform mit gesteuerter Freisetzung nach irgendeinem der vorhergehenden Ansprüche, worin die hydrophobe Substanz Talkum, Magnesiumstearat, Calciumstearat, Titanoxid, ausgefälltes Calciumcarbonat, Zinkoxid oder kolloidales Siliziumdioxid ist.

7. Dosisform mit gesteuerter Freisetzung nach irgendeinem der vorhergehenden Ansprüche, worin das Diltiazem in Form des Hydrochloridsalzes vorliegt.

8. Verfahren zur Herstellung einer Dosisform mit gesteuerter Freisetzung, welches die folgenden Schritte

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umfaßt :

(1) das Überziehen eines wasserlöslichen, Diltiazem oder Diltiazemhydrochlorid enthaltenden Kerns mit einer inneren Überzugsschicht bestehend aus Äthylcellulose und einer hydrophoben Substanz (wobei die hydrophobe Substanz ausgewählt ist aus Talkum, Erdalkalimetallstearat, Titanoxid, ausgefälltem Calciumcarbonat, Zinkoxid und kolloidalem Siliziumdioxid und das Mengenverhältnis von Äthylcellulose zur hydrophoben Substanz in einem Bereich von 1 : 1 bis 1 : 15 (bezogen auf das Gewicht) liegt), und

(2) das Überziehen des Produktes aus Stufe (1) mit einer äußeren, Diltiazem oder Diltiazemhydrochlorid enthaltenden Überzugsschicht.

9. Verfahren nach Anspruch 8, welches weiters den Schritt des Überziehens der Granula aus Schritt (1) mit einer mittleren Überzugsschicht bestehend aus Äthylcellulose alleine oder aus einer Mischung aus Äthylcellulose und einer wasserlöslichen Substanz ausgewählt aus Saccharose, Lactose, Macrogol, Mannit und Sorbit, wobei das Mengenverhältnis der wasserlöslichen Substanz zur Äthylcellulose im Bereich von 1 : 1 bis 20 : 1 (bezogen auf das Gewicht) liegt, vor dem Beschichten mit der äußeren Überzugsschicht umfaßt.

10. Verfahren nach Anspruch 8 oder Anspruch 9, worin das Diltiazem in der Form des Hydrochloridsalzes vorliegt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Dosisform mit gesteuerter Freisetzung, welches die folgenden Schritte umfaßt :

(1) das Überziehen eines wasserlöslichen, Diltiazem oder Diltiazemhydrochlorid enthaltenden Kerns mit einer inneren Überzugsschicht bestehend aus Äthylcellulose und einer hydrophoben Substanz (wobei die hydrophobe Substanz ausgewählt ist aus Talkum, Erdalkalimetallstearat, Titanoxid, ausgefälltem Calciumcarbonat, Zinkoxid und kolloidalem Siliziumdioxid und das Mengenverhältnis von Äthylcellulose zur hydrophoben Substanz in einem Bereich von 1 : 1 bis 1 : 15 (bezogen auf das Gewicht) liegt), und

(2) das Überziehen des Produktes aus Stufe (1) mit einer äußeren, Diltiazem oder Diltiazemhydrochlorid enthaltenden Überzugsschicht.

2. Verfahren nach Anspruch 1, welches weiters den Schritt des Überziehens der Granula aus Schritt (1) mit einer mittleren Überzugsschicht bestehend aus Äthylcellulose alleine oder aus einer Mischung aus Äthylcellulose und einer wasserlöslichen Substanz ausgewählt aus Saccharose, Lactose, Macrogol, Mannit und Sorbit, wobei das Mengenverhältnis der wasserlöslichen Substanz zur Äthylcellulose im Bereich von 1 : 1 bis 20 : 1 (bezogen auf das Gewicht) liegt, vor dem Beschichten mit der äußeren Überzugsschicht umfaßt.

3. Verfahren nach Anspruch 1 oder Anspruch 2, bei welchem das Mengenverhältnis des im Kern enthaltenen Diltiazems oder Diltiazemhydrochlorids zu dem in der äußeren Überzugsschicht enthaltenen Diltiazem oder Diltiazemhydrochlorid in einem Bereich von 1 : 1 bis 20 : 1 (bezogen auf das Gewicht) liegt.

4. Verfahren nach Anspruch 3, bei welchem die Teilchengröße des Diltiazem oder Diltiazemhydrochlorid enthaltenden Kerns im Bereich von 300 µm bis 2000 µm im Durchmesser liegt, das Beschichtungsverhältnis [(Gewicht von Äthylcellulose + hydrophober Substanz/Gewicht des medikamenthältigen Kerns) × 100] der inneren Überzugsschicht im Bereich von 5-50% und die Menge der in der mittleren Überzugsschicht zu verwendenden Äthylcellulose im Bereich von 0,1 bis 10% der Menge des mit einer inneren Überzugsschicht überzogenen Kerns liegt.

5. Verfahren nach Anspruch 4, bei welchem die Dosisform Granula mit einer Teilchengröße von 500 µm bis 2500 µm im Durchmesser ist.

6. Verfahren nach irgendeinem der vorhergehenden Ansprüche, bei welchem die hydrophobe Substanz Talkum, Magnesiumstearat, Calciumstearat, Titanoxid, ausgefälltes Calciumcarbonat, Zinkoxid oder kolloidales Siliziumdioxid ist.

7. Verfahren nach irgendeinem der vorhergehenden Ansprüche, worin das Diltiazem in Form des Hydrochloridsalzes vorliegt.