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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



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Aviso: En el plazo de nueve meses a contar desde la fecha de publicación en el Boletín europeo de patentes, de la mención de concesión de la patente europea, cualquier persona podrá oponerse ante la Oficina Europea de Patentes a la patente concedida. La oposición deberá formularse por escrito y estar motivada: sólo se considerará como formulada una vez que se haya realizado el pago de la tasa de oposición (art. 99.1 del Convenio sobre concesión de Patentes Europeas).

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Como "selectivo" se designa en el marco de la presente invención a aquellos inhibidores del factor Xa de la coagulación sanguínea en los que los valores CI_{50} para la inhibición del factor Xa respecto a los valores CI_{50} para la inhibición de otras serinaproteasas, en especial de la trombina, plasmina y tripsina, son alrededor de 100 veces, preferiblemente alrededor de 500 veces, en especial alrededor de 1.000 veces, menores, en donde en lo que respecta a los métodos de ensayo para la selectividad se remite a los métodos de ensayo de los Ejemplos A-1)a.1) y a.2) descritos más adelante.

Los compuestos de fórmula general (I) conforme a la invención pueden utilizarse además para impedir la coagulación sanguínea *ex vivo*, p.ej. en sangre conservada o en muestras biológicas que contienen factor Xa.

Son por consiguiente objeto de la presente invención oxazolidinonas de fórmula (I) que en especial tienen una actividad inesperada, intensa y selectiva de inhibición del factor Xa.

Son por consiguiente también otro objeto de la presente invención medicamentos y composiciones farmacéuticas que contienen al menos un compuesto de fórmula general (I) conforme a la invención junto con uno o varios coadyuvantes o vehículos farmacéuticamente inocuos y utilizables para las indicaciones anteriormente citadas.

Además la presente invención se refiere a un procedimiento para la profilaxis y/o tratamiento de enfermedades del cuerpo humano o animal, en especial de las enfermedades anteriormente indicadas utilizando los compuestos de fórmula general (I) conforme a la invención.

Además la presente invención comprende también un procedimiento para impedir la coagulación sanguínea *in vitro*, en especial en sangre conservada o en muestras biológicas que contienen factor Xa, caracterizado porque se añaden compuestos de fórmula general (I).

Para la administración de los compuestos conforme a la invención se consideran todas las formas de administración habituales. Preferiblemente la administración se realiza por vía oral, lingual, sublingual, bucal, rectal o parenteral (es decir eludiendo el tracto intestinal, o sea intravenosa, intraarterial, intracardiaca, intracutánea, subcutánea, transdérmica, intraperitoneal o intramuscular). Son especialmente adecuadas la administración oral e intravenosa. Es muy especialmente preferida la administración oral, en lo que radica otra ventaja frente a la terapia de enfermedades tromboembólicas conocida del estado de la técnica.

Los nuevos principios activos de fórmula general (I) pueden transformarse de modo conocido en las formulaciones habituales, como comprimidos, grageas, píldoras, granulados, aerosoles, jarabes, emulsiones, suspensiones y soluciones, utilizando vehículos o disolventes inertes, no tóxicos, farmacéuticamente adecuados. A este respecto el compuesto terapéuticamente activo debe estar presente a una respectiva concentración de aproximadamente 0,1 a 95% en peso, preferiblemente de 0,5 a 90% en peso, en especial de 1 a 85% en peso de la mezcla total, es decir en cantidades que sean suficientes para conseguir la amplitud de dosificación indicada.

Sin embargo, dado el caso, puede ser preciso desviarse de las cantidades indicadas, y concretamente en función del peso corporal o del tipo de vía de administración, del comportamiento individual frente al medicamento, del tipo de formulación y del momento o intervalo a los que se realice la administración. Así, en algunos casos puede ser suficiente con menos de la cantidad mínima antes indicada, mientras que en otros caso deben sobrepasarse los límites superiores anteriormente indicados. En el caso de la administración de cantidades mayores puede ser recomendable dividir estas en varias tomas individuales a lo largo del día.

Las formulaciones se preparan por ejemplo cortando los principios activos con disolventes y/o vehículos, dado el caso utilizando emulsionantes y/o dispersantes, pudiéndose utilizar p.ej. en el caso de la utilización de agua como diluyente dado el caso disolventes orgánicos como diluyente coadyuvante.

En general ha mostrado ser ventajoso en la administración intravenosa administrar cantidades de aproximadamente 0,001 a 10 mg/kg, preferiblemente de aproximadamente 0,01 a 10 mg/kg, en especial de aproximadamente 0,1 a 8 mg/kg de peso corporal, para la consecución de resultados eficaces.

En general ha mostrado ser ventajoso en la administración oral administrar cantidades de aproximadamente 0,01 a 50 mg/kg, preferiblemente de aproximadamente 0,1 a 10 mg/kg, en especial de aproximadamente 0,5 a 8 mg/kg de peso corporal, para la consecución de resultados eficaces.

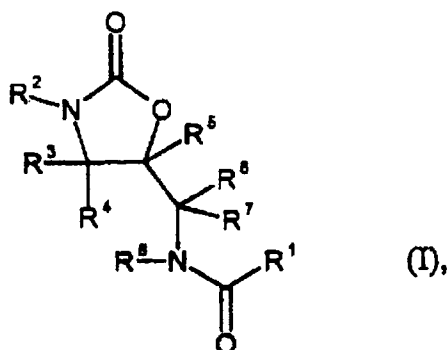
Sin embargo, dado el caso, puede ser preciso desviarse de las cantidades anteriormente indicadas, y concretamente en función del peso corporal o del tipo de vía de administración, del comportamiento individual frente al medicamento, del tipo de formulación y del momento o intervalo a los que se realice la administración. Así, en algunos casos puede ser suficiente con menos de la cantidad mínima antes indicada, mientras que en otros casos deben sobrepasarse los límites superiores anteriormente indicados. En el caso de la administración de cantidades mayores puede ser recomendable dividir estas a lo largo del día, concretamente en varias tomas individuales o como infusión permanente.

Los compuestos de fórmula general (I) conforme a la invención - incluidos también los compuestos excluidos de protección de producto por renuncia - se caracterizan frente a los preparados habituales para el tratamiento de enfermedades tromboembólicas especialmente porque mediante la inhibición selectiva del factor Xa se consigue una

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REIVINDICACIONES

1. Compuesto de fórmula general (I) de fórmula general (I)



en la que:

R¹ representa 2-tiofeno que está substituido en la posición 5 con un resto del grupo de cloro, bromo, metilo o trifluorometilo,

R² representa D-A:

en el que:

el resto "A" representa fenileno;

el resto "D" representa un heterociclo saturado de 5 ó 6 eslabones,

que está enlazado a través de un átomo de nitrógeno con "A"

que posee directamente adyacente al átomo de nitrógeno de enlace un grupo carbonilo y

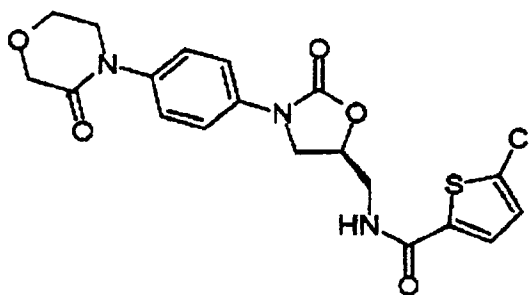
en el que un carbono miembro del anillo puede estar remplazado por un heteroátomo de la serie de S, N y O;

pudiendo estar el grupo "A" anteriormente definido dado el caso mono o disubstituido en la posición meta respecto al enlace con la oxazolidinona con un resto del grupo de flúor, cloro, nitro, amino, trifluorometilo, metilo o ciano,

R³, R⁴, R⁵, R⁶, R⁷ y R⁸ representan hidrógeno,

y sus sales, hidratos, hidratos de las sales y profármacos farmacéuticamente aceptables.

2. Compuesto conforme a la reivindicación 1 de la fórmula siguiente



y sus sales, hidratos, hidratos de las sales y profármacos farmacéuticamente aceptables.

3. Procedimiento para la preparación de oxazolidinonas substituidas como las definidas en las reivindicaciones 1 ó 2, en el que

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en la que

los restos R¹, R², R³, R⁴, R⁵, R⁶, R⁷ y R⁸ tienen los significados indicados en la reivindicación 1.

5 4. Medicamentos que contienen al menos un compuesto como los definidos en las reivindicaciones 1 ó 2 así como uno o más coadyuvantes o vehículos farmacológicamente inocuos.

10 5. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para la fabricación de medicamentos o composiciones farmacéuticas para la profilaxis y/o tratamiento de enfermedades tromboembólicas, en especial infarto cardiaco, angina de pecho (incluida la angina inestable), reoclusiones y reestenosis tras una angioplastia o bypass aortocoronario, apoplejía cerebral, ataques isquémicos transitorios, enfermedades oclusivas arteriales periféricas, embolias pulmonares o trombosis venosas profundas.

15 6. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para la fabricación de medicamentos o composiciones farmacéuticas para la profilaxis y/o tratamiento de enfermedades que se ven influidas positivamente mediante la inhibición del factor Xa.

20 7. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para la fabricación de medicamentos o composiciones farmacéuticas para el tratamiento de la coagulación intravascular diseminada (DIC).

8. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para la fabricación de medicamentos o composiciones farmacéuticas para la profilaxis y/o tratamiento de enfermedades como aterosclerosis; artritis; enfermedad de Alzheimer o cáncer.

25 9. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para la fabricación de medicamentos o composiciones farmacéuticas para la inhibición del factor Xa.

30 10. Procedimiento para impedir la coagulación sanguínea *in vitro*, en especial en sangre conservada o en muestras biológicas que contienen factor Xa, **caracterizado** porque se añaden compuestos como los definidos en las reivindicaciones 1 ó 2.

11. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para impedir la coagulación sanguínea *ex vivo*.

35 12. Uso de compuestos como los definidos en las reivindicaciones 1 ó 2 para impedir la coagulación *ex vivo* en muestras biológicas que contienen el factor Xa de coagulación sanguínea.

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(12) **United States Patent**
Kettelhoit et al.

(10) **Patent No.:** **US 6,294,201 B1**
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(54) **OSMOTIC MEDICAMENT RELEASING
SYSTEM**

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U.S.C. 154(b) by 0 days.

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§ 102(e) Date: **Apr. 25, 2000**

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A61K 9/26; A61K 9/14

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424 484; 424 486; 424/488

(58) **Field of Search** 424,464, 473,
424/484, 486, 488, 469

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(57) **ABSTRACT**

This invention relates to an orally administered osmotic drug release system that consists of a shell and a core containing a pharmaceutically active substance, as well as a process for its production. The invention relates further to an osmotic drug release system for use as a drug in human beings and animals, as well as the use of the osmotic drug release system in the production of a drug for the treatment and/or prevention of illnesses in human beings and animals.

17 Claims, No Drawings

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OSMOTIC MEDICAMENT RELEASING SYSTEM

This application is a 371 PCT/EP98 06454 filed Oct. 12, 1998.

This invention relates to an orally administered osmotic drug release system that consists of a shell and a core containing a pharmaceutically active substance, as well as a process for its production. The invention relates further to an osmotic drug release system for use as a drug in human beings and animals, as well as the use of the osmotic drug release system in the production of a drug for the treatment and/or prevention of illnesses in human beings and animals.

In principle, osmotic drug release systems are known in the state of the art. Osmotic pressure is generally used as the energy source for delivering the active ingredient of a drug to the surrounding medium at a controlled rate. Consequently, these types of systems are referred to as osmotic pumps. A comprehensive overview of osmotic drug release systems can be found in *Journal of Controlled Release* 35 (1995), 1-21, where a basic distinction is drawn between multiple-chamber systems and single-chamber systems. In its most basic form, the single-chamber system consists of a conventional tablet comprising a shell made of a semi-permeable membrane with an outlet, as well as a core containing the active ingredient in solid form. Following oral administration, water passes into the core through the semi-permeable membrane and dissolves the active ingredient, which is then released through the outlet (U.S. Pat. No. 3,845,770). However, this principle is only suitable for use with highly water-soluble active ingredients, as these are the only active ingredients capable of generating sufficiently high osmotic pressure. Consequently, so-called double-chamber systems ("push-pull" systems) were developed specifically for poorly soluble active ingredients (U.S. Pat. No. 4,111,202; European patent application no. 52 917). However, the production of such two-chamber systems is highly complex in technical terms. Consequently, the single-chamber system possesses a fundamental advantage over multiple-chamber systems. To utilize the advantages of the single-chamber system for poorly soluble drugs while achieving sufficient osmotic pressure in the interior of the tablet, single-chamber systems were proposed in which a core consists of the active ingredient and certain polymeric swelling agents which, upon the addition of water, expand through the outer semi-permeable membrane and are released together with the active ingredient, which is partially suspended in the swelling agent. The selection of certain polymeric swelling agents is of decisive importance in this system, as certain swelling agents, as has been described in EP-A-0 277 092, such as polyvinyl pyrrolidone, polyethylene oxide or polymethylacrylate produce so much expansion pressure that the semi-permeable shell membrane bursts open completely after a short time and the active ingredient is released within a short period of time instead of being released in a delayed or controlled manner, as desired. Thus, to solve this problem, EP-A-0 277 092 provides for a specific selection of hydrophilic polymeric swelling agents, namely a mixture of a vinyl pyrrolidone - vinyl acetate copolymer and an ethylene oxide homopolymer.

WO 96/40080 claims generic protection for osmotic single-chamber systems comprising a core made of a pharmaceutical active ingredient, a water-soluble osmotic agent and a water-expandable polymer. However, as has already been specified in EP-A-0 277 092, not all polymeric hydrophilic swelling agents are suited for use in these single-chamber systems, and a careful selection must be made to

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ensure that the active substance is released from the single-chamber system in a controlled manner, as desired. In the concrete forms of execution of WO 96/40080, polyethylene oxide and cellulose, or derivatives thereof, are among the materials used as water-expandable polymers.

An osmotic drug release system with controlled, i.e., generally delayed release, that consists of a single-chamber system should, in principle, allow for maximum release of the active ingredient without the outlet being torn open during release and resulting in uncontrolled release of the active ingredient. However, a common problem among single-chamber systems is that a substantial portion of the active ingredient remains in the tablet, as insufficient osmotic pressure is generated in the interior of the tablet to fully release the active ingredient. Thus, a disadvantage of the systems described above is that they do not fully release the active substance from the shell membrane and through the outlet, so that relatively large component of the active substance is not absorbed and is excreted unused. However, the use of a water-expandable polymer that generates substantial osmotic pressure may result in the tablet being torn open or even bursting, thus preventing delayed, controlled release from being achieved.

Another problem commonly found in osmotic drug release systems known in the art is that the uncoated tablet cores lack sufficient mechanical stability, which makes them difficult to coat.

In principle, an osmotic drug release system should be easily manufactured, consist of reasonably priced and pharmacologically tolerable materials, and allow for the release of the active ingredient in an advantageous manner.

Surprisingly, it was found that the use of a combination of two specific hydrophilic water-expandable polymers as core components, at specific weight proportions, is particularly suited for achieving the aforementioned desired attributes of an osmotic single-chamber drug release system that contains a pharmaceutically active substance, preferably a dihydropyridine as its active ingredient. The inventors of this invention found that a combination of the heteropolysaccharide xanthan and a vinyl pyrrolidone—vinyl acetate copolymer as water-expandable polymers in specific weight concentrations allows for the virtually complete release of the active substance from the shell without resulting in the outlet being torn open and the active ingredient being released in an uncontrolled manner.

Without relying on theoretical constraints, it is assumed that the highly favorable release properties of the combination between xanthan and the vinyl pyrrolidone—vinyl acetate copolymer are due, in particular, to the fact that it forms structurally viscous solutions, the viscosity of which decreases during flow in response to increasing transverse strain. Apparently, this allows for especially uniform release of the active substance from the outlet without the membrane being torn open, so that the active substance is released uniformly and almost completely over a relatively long period of time.

When used as a water-expandable polymer, xanthan also possesses the advantage of being easier to handle than the polyethylene oxides used in EP-A-0 277 092 and WO 96/40080, as it does not induce the so-called TOMS effect (reduction in frictional resistance). Another advantage associated with the use of xanthan in comparison with the use of polyethylene oxide as a water-expandable polymer consists in the fact that polyethylene oxides are generally only wet-granulated with organic solvents (as, for example, in EP-A-0 277 092), so that explosion protection measures must be taken during production; alternatively, tablets must

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- 15 to 35% in weight of a pharmaceutically active substance
 20 to 50% in weight of xanthan
 10 to 30% in weight of a vinyl pyrrolidone—vinyl acetate copolymer
 wherein additional components selected from a group consisting of other hydrophilic expandable polymers, osmotically active additives and pharmaceutically acceptable additive materials may also be contained in said core so that the sum of the core components totals 100% in weight, wherein the percent in weight figures refer to the total weight of the core components.
2. Osmotic drug release system according to claim 1, which includes a core comprising:
- (a) 20 to 30% in weight of a pharmaceutically active substance
 (b) 25 to 40% in weight xanthan
 (c) 10 to 20% in weight of a vinyl pyrrolidone—vinyl acetate copolymer
 wherein additional components selected from a group consisting of other hydrophilic expandable polymers, osmotically active additives and pharmaceutically acceptable additive materials may also be contained in said core so that the sum of the core components totals 100% in weight, wherein the percent in weight figures refer to the total weight of the core components.
3. Osmotic drug release system according to claim 1 characterized in that the core contains at least one osmotically active additive.
4. Osmotic drug release system according to claim 1 characterized in that the core contains at least one osmotically active additive, as well as at least one pharmaceutically acceptable additive material.
5. Osmotic drug release system according to claim 1 which includes a core comprising:
- 20 to 30% in weight of a pharmaceutically active substance
 25 to 40% in weight of xanthan
 10 to 20% in weight of a vinyl pyrrolidone—vinyl acetate copolymer
 10 to 30% in weight of an osmotically active substance
 8 to 20% in weight of at least one pharmaceutically acceptable additive material with the percent in weight figures referring to the total weight of the core components, and the sum of the core components totaling 100%.
6. Osmotic drug release system according to claim 1 characterized in that the active ingredient is a sparingly soluble active substance.

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7. Osmotic drug release system according to claim 1 characterized in that the active ingredient is an active substance which is still absorbed in the colon.
8. Osmotic drug release system according to claim 1 characterized in that the active ingredient is a dihydropyridine.
9. Osmotic drug release system according to claim 1 characterized in that the active ingredient is nifedipine.
10. Osmotic drug release system according to claim 1 characterized in that the osmotically active additive is sodium chloride.
11. Osmotic drug release system according to claim 1 characterized in that the pharmaceutically acceptable additive material is selected from the group consisting of pharmaceutically acceptable buffer materials, pharmaceutically acceptable lubricants, pharmaceutically acceptable disintegrants, and pharmaceutically acceptable tablet-making process materials.
12. Osmotic drug release system according to claim 11, characterized in that the pharmaceutically acceptable buffer material is sodium bicarbonate, the pharmaceutically acceptable lubricant is magnesium stearate, the pharmaceutically acceptable disintegrant agent is sodium carboxy methyl starch, and a pharmaceutically acceptable tablet-making process material.
13. Osmotic drug release system according to claim 1 which includes a core comprising:
- 19 to 23% in weight of a pharmaceutically active substance
 28 to 32% in weight of xanthan
 15 to 20% in weight of a vinyl pyrrolidone—vinyl acetate copolymer
 15 to 20% in weight of sodium chloride
 5 to 7% in weight of sodium bicarbonate
 6 to 9% in weight of sodium carboxy methyl starch
 <1% in weight of magnesium stearate
 with the percent in weight figures referring to the total weight of the core components, and the sum of the core components totaling 100%.
14. Osmotic drug release system according to claim 1 characterized in that it is present in tablet form.
15. Procedure for the production of the osmotic drug release system according to claim 1 characterized in that the components of the core are mixed together, possibly wet-granulated or dry-granulated, and made into tablets, and that the resulting core is coated with the shell.
16. Osmotic drug release system according to claim 1 for use as a drug in human beings and animals.
17. A method of treating high blood pressure, coronary heart disease, or cerebral performance disorders, and for therapy of neurological deficits following subarachnoid hemorrhage, comprising administering to a patient in need thereof an osmotic drug release system according to claim 1.

* * * * *

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EXAMPLES 1 and 2 (tablets with dry-granulated components)

Composition

Core

	1	2
Nifedipine	36.00mg	36.00mg
Xanthan (Rhodigel® commercial product, Meyhall)	50.96mg	50.96mg
Copolyvidone (Kollidon® VA64, commercial product, BASF, vinyl pyrrolidone - vinyl acetate copolymer)	29.45mg	29.45mg
Sodium chloride	28.71mg	28.71mg
Sodium bicarbonate	10.15mg	10.15mg
Sodium carboxy methyl starch	12.74mg	12.74mg
Aerosil	0.85mg	0.85mg
Magnesium stearate	0.68mg	0.68mg
Shell (osmotic membrane):		
Cellulose acetate	8.45mg	11.40mg
Polyethylene glycol 3350	0.45mg	0.60mg
Approximate tablet weight	178.5 mg	181.6 mg
Tablet format	6r9 mm	6r9 mm

Production Process

Nifedipine, Kollidon® VA64 (70% in weight of the above mass), Rhodigel®, sodium chloride and sodium bicarbonate were mixed together and then dry-granulated. The granulate was subsequently made into tablets. The tablet cores were coated with an organic coating containing the components of the osmotic membrane. The coated tablets were subsequently dried. The diameter of the resulting tablets was 6 mm.

Subsequently, an opening of approx. 800 μ m in diameter was made into each tablet with a hand drill.

Examples 3 and 4 (tablets with wet-granulated components)

Composition

Core

	1	2
Nifedipine	36.00mg	36.00mg
Xanthan (Rhodigel® commercial product, Meyhall)	50.96mg	50.96mg
Copolyvidone (Kollidon® VA64, commercial product, BASF, vinyl pyrrolidone - vinyl acetate copolymer)	29.45mg	29.45mg
Sodium chloride	28.71mg	28.71mg
Sodium bicarbonate	10.15mg	10.15mg
Sodium carboxy methyl starch	12.74mg	12.74mg
Aerosil	0.90mg	0.90mg
Magnesium stearate	0.50mg	0.50mg

Shell (osmotic membrane)

Cellulose acetate	7.50 mg	9.45 mg
Polyethylene glycol 3350	0.40 mg	0.50 mg

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-continued

Approximate tablet weight	177 mg	179 mg
Tablet format	6r9 mm	7r10 mm

Production Process

Rhodigel®, sodium chloride, sodium bicarbonate and sodium carboxy methyl starch were mixed together and then wet-granulated with a suspension of nifedipine and Kollidon® VA64 in water. The granulate was then mixed with aerosil and magnesium stearate. The mixture was subsequently made into tablets. The tablet cores were coated with an organic coating containing the components of the osmotic membrane. The coated tablets were subsequently dried. The diameter of the resulting tablets was 6 mm and 7 mm, respectively.

Two openings, each with a diameter of approx. 600 μ m, were subsequently made into each tablet with a hand drill.

Reference Example 1 (corresponds to example 3 in EP-A-0277092)

Composition

Core

Nifedipine	50.00mg
Polyox coagulant	26.0 mg
Copolyvidone (Kollidon® VA64, commercial product, BASF, vinyl pyrrolidone - vinyl acetate copolymer)	18.02mg
Sodium chloride	20.02mg
Magnesium stearate	2.00mg

Shell (osmotic membrane)

Cellulose acetate	11.20 mg
Polyethylene glycol 4000	1.50 mg
Approximate tablet weight	122.7 mg
Tablet format	7r10 mm

Production Process

Nifedipine, polyox coagulant, Kollidon® VA64, sodium chloride and magnesium stearate were mixed together. However, to avoid the use of organic solvents, the mixture was then made into tablets without prior granulation. The tablet cores were coated with an organic coating containing the components of the osmotic membrane. To avoid the use of chlorinated carbohydrates, cellulose acetate type 398-10 was used instead of cellulose acetate type 320S. The coated tablets were subsequently dried. The diameter of the resulting tablets was 7 mm.

Subsequently, an opening of approx. 800 μ m in diameter was made into each tablet with a hand drill.