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(54) **NEW POLYMORPHIC FORM OF CRYSTALLINE ROSUVASTATIN CALCIUM&NOVEL PROCESSES FOR CRYSTALLINE AS WELL AS AMORPHOUS ROSUVASTATIN CALCIUM**

NEUE POLYMORPHE FORM VON KRISTALLINEM ROSUVASTATIN-CALCIUM UND NEUARTIGE VERFAHREN FÜR KRISTALLINES SOWIE AMORPHES ROSUVASTATIN-CALCIUM

NOUVELLE FORME POLYMORPHE DE ROSUVASTATINE CALCIQUE CRISTALLINE ET NOUVEAUX PROCÉDÉS POUR LA ROSUVASTATINE CALCIQUE CRISTALLINE ET AMORPHE

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EP 3 445 751 B9

Description

REFERENCE:

[0001] This application is a **Patent of Addition** filed under section 54 and rule 13(3) of the Indian Patents Act, 1970 to Indian patent application no.: 1556/DEL/2011 filed on June 01, 2011.

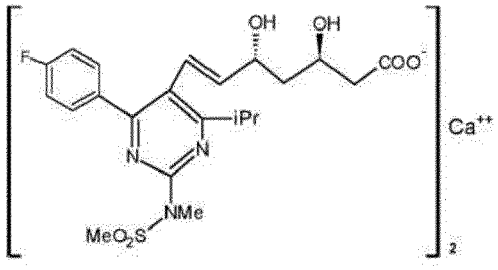
[0002] The invention comprises an improvement in and a modification of the invention claimed in the specification of the main patent applied for.

FIELD OF INVENTION:

[0003] The present invention relates to a process for the preparation of a new polymorphic form of crystalline Rosuvastatin calcium, which is used to treat a disease condition wherein inhibition of HMG COA reductase is beneficial.

BACKGROUD OF INVENTION:

[0004] Rosuvastatin calcium is known by its chemical name as 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methyl sulfonyl amino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt of formula I as given below.



FORMULA I

which is known to inhibit the HMG-CoA reductase, and subsequently suppress the bio synthesis of cholesterol. Rosuvastatin calcium is useful in the treatment of hyper cholesterolemia, hyperlipoproteinemia, and atherosclerosis. Rosuvastatin calcium may form hydrates with a varying content of water.

[0005] EP-A1-0521471 describes in the preparation of Rosuvastatin calcium in powder form. Rosuvastatin sodium is dissolved in water at room temperature and an aqueous calcium chloride solution is added dropwise. The collected precipitate is an amorphous powder.

[0006] US.Pat. No 6,777,552 discloses the preparation of Rosuvastatin calcium through hydrolysis of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxy-(E)-6-heptanoate with calcium hydroxide in a water /ethanol solution.

[0007] WO 00/42024 discloses a crystalline form, hereafter referred to as Form A of -[4-(4-flurophen yl)-6-isopropyl-2-(N-methyl-N-methyl sulfonyl amino)-pyrimidin-5-yl]- (3R,5S) - dihydroxy-hcpt-6-cnoic acid calcium salt and hydrates thereof, which arc prepared by dissolving amorphous Rosuvastatin calcium form in a mixture of water and an organic solvent such as acetone or acetonitrile under heating and then cooling the solution to precipitate crystalline Form A.

[0008] WO 2005/023779 discloses another crystalline form, hereafter referred to as Form B of 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt which is prepared by slurrying of Amorphous Rosuvastatin calcium in water at 40°C to get crystalline Form B. US20080194604 describes another new process for the preparation.

[0009] US 20080194604 discloses another crystalline form, hereafter referred to as Form C of 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid calcium salt.

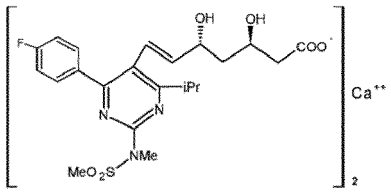
[0010] Crystalline forms often show desired different physical and/or biological characteristics which may assist in the manufacturing or formulation of the active compound, to the purity levels and uniformity required for regulatory approval. Crystalline forms of such active compounds may also possess improved pharmacological characteristics, for example, improved bioavailability, and therefore, novel crystalline forms offer enhanced possibilities to modulate and design improved drug products. As crystalline forms A, B,

[0011] C etc of Rosuvastatin calcium involves very tedious processes which are difficult to use at plant level since the material becomes sticky when stirred initially, results dull colour of material and the product does not crystallize after adding anti-solvent if dissolved in the solvent used. Some of these forms have very high water content which can affect

the stability of the product, therefore there was a need for other crystalline forms of 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5 S)-dihydroxy-hept-6-enoic acid calcium salt or Rosuvastatin Calcium of improved colour having low water content & simplified process which is easy to handle at plant level, to have a sufficient diversity on crystalline materials to optimize manufacture, formulation and biological efficiency.

SUMMARY OF INVENTION:

[0012] This invention provides a process for the preparation of a highly pure crystalline form "M" of the compound 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt designated as form "M" of Rosuvastatin calcium of formula I or hydrates thereof:



Formula I

wherein the polymorphic crystalline form M of Rosuvastatin Calcium has characteristic peaks as given below:

2- Theta	Relative intensity (%) (Peaks having > 40% Intensity are mentioned)
6.83	63
8.14	49
9.15	73
10.23	43
11.30	95
15.60	42
17.82	48
19.17	100
19.44	68
20.30	80
20.82	80
22.01	65
22.85	74
24.14	56
24.56	40

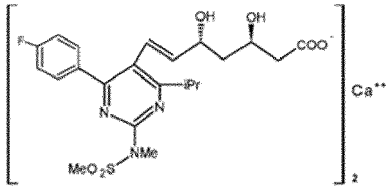
which comprises:

i. Deprotection of tert-butyl-2-((4R,6S)-6-((E)-2-(4(-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulphonamido)pyrimidin-5-yl)vinyl)-2,2- dimethyl-1,3-dioxan-4-yl) acetate in acetonitrile using dilute hydrochloric acid.
ii. Hydrolysis of resulting material with aqueous Caustic solution.
iii. Complete removal of acetonitrile from reaction mass under vacuum.
iv. Addition of water & methyl tert-butyl ether.
v. Layer separation.
vi. Isolation of Rosuvastatin calcium by addition of calcium chloride to aqueous layer.
vii. Recrystallization of resulting Rosuvastatin Calcium (wet or dry) by dissolving the product using an aliphatic ketone such as acetone, ethyl methyl ketone, diethyl ketone, dipropyl ketone, dibutyl ketone or mixture thereof &

recrystallization by adding water as anti-solvent.
viii. Isolation of novel Rosuvastatin calcium crystalline form M by routine filtration & drying;

wherein the anti-isomer content is very low (<0.1% by HPLC) or even 'Not Detected'.

[0013] Further, the invention also provides a process for the preparation of a highly pure crystalline form "M" of the compound 7 -[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt designated as form "M" of Rosuvastatin calcium of formula I or hydrates thereof:



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19.17	100
19.44	68
20.30	80
20.82	80
22.01	65
22.85	74
24.14	56
24.56	40

which comprises:
the step of recrystallization of resulting Rosuvastatin Calcium (wet or dry) by dissolving the product using an aliphatic ketone such as acetone, ethyl methyl ketone, diethyl ketone, dipropyl ketone, dibutyl ketone or mixture thereof & recrystallization by adding water as anti-solvent, wherein the ratio of aliphatic Ketone & Water can be selected from 10:5, 5:5 or even 3:8.

[0014] Furthermore, the disclosure also reports the novel processes for the preparation of stable crystalline as well as amorphous Rosuvastatin calcium as confirmed by their XRD as well as stability data.

DETAILED DESCRIPTION OF THE INVENTION:

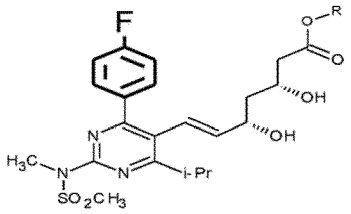
[0015] The main aspect of the present invention is to provide a process for the preparation of a crystalline polymorphic forms of 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]- (3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt (Rosuvastatin Calcium) of high purity which exhibits a characteristic X-Ray diffraction pattern with characteristic peaks expressed in 2^{Θ} values & relative intensity as given below in tabular form), hereinafter designated

as form M. XRD diffractogram of Rosuvastatin calcium form M is attached as figure I.

2- Theta	Relative intensity (%) (only greater then 40 % mentioned)
6.83	63
8.14	49
9.15	73
10.23	43
11.30	95
15.60	42
17.82	48
19.17	100
19.44	68
20.30	80
20.82	80
22.01	65
22.85	74
24.14	56
24.56	40

[0016] An exemplary process, which does not correspond to the invention as defined in the claims, but it is useful for the understanding of the claimed process thereof, for preparing a highly pure crystalline form M of Rosuvastatin Calcium of formula I comprises:

a) Hydrolysis of Rosuvastatin tert butyl or methyl ester of formula II in presence of aq. Caustic solution in methanol.



R=Methyl or tert-butyl

Chemical Name: tert-Buty or methyl-(6E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoate

Formula II

b) Washing of reaction mass with methyl tert butyl ether.
c) treatment of aq. layer with hydrochloric acid followed by addition of calcium chloride to the reaction mass.
d) isolation of Rosuvastatin calcium by filtration & optionally drying.
e) dissolution of Rosuvastatin calcium (dry or wet) material in an aliphatic ketone.
f) crystallization of material by adding water.
g) filtration of resulting solid followed by drying to get new polymorphic form of Crystalline Rosuvastatin calcium

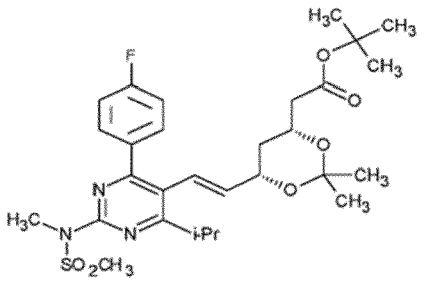
designated as form M.

[0017] According to another aspect, the ketone used is selected from acetone, ethyl methyl ketone, diethyl ketone, dipropyl ketone, dibutyl ketone or a mixture thereof & water.

[0018] Furthermore, the ratio of aliphatic Ketone used in step e) & Water used in step f) can be 10:5, 5:5 or even 3:8.

[0019] According to an aspect of the present invention, a process for highly pure crystalline form M of Rosuvastatin Calcium of formula I which comprises:

a) Deprotection of Rosuvastatin diprotected tert butyl ester of formula III in acetonitrile using dil Hydrochloric acid at room temperature.



Chemical Name: tert-butyl-2-((4R,6S)-6-((E)-2-(4(-(4-fluorophenyl)-6-isopropyl-2-(N-methyl methylsulphonamido)pyrimidin-5-yl) vinyl)-2,2-dimethyl-l,3-dioxan-4-yl)acetate

Formula III

b) Confirmation of reaction completion after 2-4 hours via TLC/HPLC.
c) Hydrolysis of reaction mass in presence of aq. Caustic solution.
d) Again confirmation of reaction completion after 4-5 hours via TLC/HPLC.
e) Complete recovery of solvent using vacuum
f) Addition of water & methyl tert butyl ether and stirring for 10-15 min.
g) Layer separation
h) Slow addition of calcium chloride solution to reaction mass
i) Stirring for 4-6 hours
j) Isolation of product via filtration & drying at 50-60 °C.
k) Dissolution of Rosuvastatin calcium (dry or wet) of step j) in an aliphatic ketone.
l) Crystallization of material by adding water.
m) filtration of resulting solid followed by drying to get new polymorphic form of Crystalline Rosuvastatin calcium designated as form M.

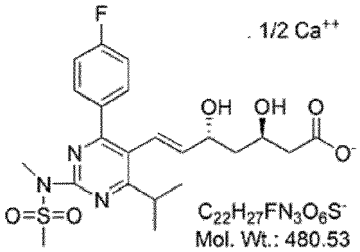
[0020] According to another aspect, the ketone used is selected from acetone, ethyl methyl ketone, diethyl ketone, dipropyl ketone, dibutyl ketone or a mixture thereof.

[0021] According to one more aspect of current invention, the ratio of aliphatic Ketone used in step e) & Water used in step f) can be 10:5, 5:5 or even 3:8.

[0022] According to one more aspect of current invention, the form M is stable at 30°C with 65%RH for 48 months & 40°C with 75%RH for 6 months for all ICH/EP/USP grade. The stability data is as shown in the table below.

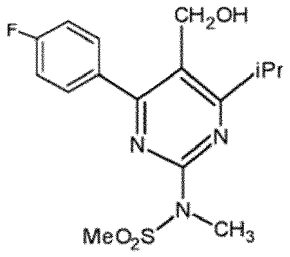
Storage condition	Storage Period (Months)	Description	Assay (OAB)	Related Substances (HPLC)								Water
				Anti-isomer	Lactone	Methyl Ester	Tert Butyl Ester	Diprotected	RT-08	RT-07	Individual Unknown Imp.	Total Imp.	
	Limits →	**A White to creamish solid**	**98.0-102.0% w/w**	**NMT 0.15%**	**NMT 0.15%**	**NMT 0.15 %**	**NMT 0.15 %**	**NMT 0.15 %**	**NIMT 0.15 %**	**NMT 0.15 %**	**NMT 0.1%**	**NMT 1.5%**	**NMT 8.0%**
40°C/ 75% RH	Initial	A white solid	100.08	ND	0.02	ND	ND	ND	ND	0.05	0.02	0.13	5.06
	1	A white solid	100.03	ND	0.04	ND	ND	ND	ND	0.05	0.03	0.14	5.65
	2	A white solid	99.93	ND	0.04	ND	ND	ND	ND	0.05	0.02	0.15	5.59
	3	A white solid	100.03	ND	0.04	ND	ND	ND	ND	0.05	0.02	0.13	5.66
	6	A white solid	99.59	ND	0.04	ND	ND	ND	ND	0.04	0.02	0.12	5.63
30°C/ 65% RH	3	A white solid	99.58	ND	0.05	ND	ND	ND	ND	0.05	0.02	0.16	5.30
	6	A white solid	99.54	ND	0.04	ND	ND	ND	ND	0.05	0.04	0.14	5.43
	9	A white solid	99.33	ND	0.04	ND	ND	ND	ND	0.05	0.02	0.14	3.44
	12	A white solid	99.55	0.04	0.05	ND	ND	ND	ND	0.06	0.02	0.17	5.55
	18	A white solid	99.70	0.03	0.04	ND	ND	ND	ND	0.05	0.02	0.16	5.57
	24	A white solid	99.81	0.04	0.04	ND	ND	ND	ND	0.05	0.02	0.15	5.72
	36	A white solid	99.75	0.04	0.04	ND	ND	ND	ND	0.05	0.02	0.16	5.74
	48	A white solid	99.66	0.05	0.04	ND	ND	ND	ND	0.05	0.02	0.16	5.90

[0023] According to yet another important aspect of current invention, the anti-isomer content in Rosuvastatin calcium is very low or even not detected in comparison to other processes reported in prior art.



Rosuvastatin Calcium Anti-Isomer (Formula IV)

[0024]



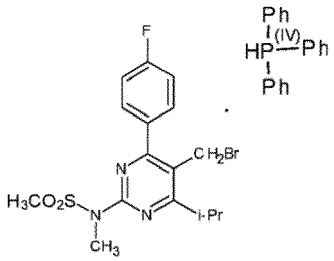
4-(4-fluorophenyl)-6-isopropyl -2-[(N -methyl -N -methylsulfonyl) amino] pyrimidine-5-yl-methanol

[0025]

Mol For: $C_{16}H_{20}O_3FN_3S$

For Wt: 353.41

(Intermediate A)



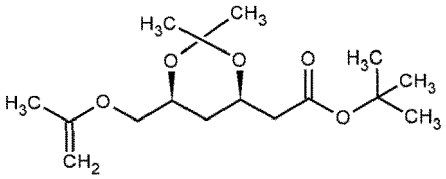
N-[4-(4-fluorophenyl)-5-(bromomethyl)-6-(isopropylpyrimidin-2-yl)-N-methyl methane sulfonamide triphenylphosphonium salt

[0026]

Mol For: $C_{14}H_34BrFN_3O_2PS$

For Wt: 678.59

(Intermediate B)



tert-Butyl(4R-cis)-6-[(acetyloxy)methyl]-2, 2-dimethyl-1,3 -dioxane-4-acetate

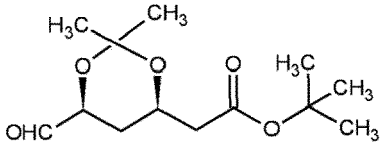
CAS# 154026-95-6

Mol For.: $C_{15}H_{26}O_6$

For. Wt.: 302.36

[0027]

(Intermediate C)



(4R-cis)-6-Formaldehydel-2,2-dimethyl 1,3dioxane-4-acetic-acid,1,1-dimethylethyl ester

CAS# 124752-23-4

Mol For.: $C_{13}H_{22}O_5$

For. Wt: 258.31

(Intermediate D)

[0028] According to an exemplary process, which does not correspond to the invention as defined in the claims, but it is useful for the understanding of the claimed processes thereof, for preparation of stable amorphous Rosuvastatin Calcium which comprises:

a) dissolution of any crystalline form of Rosuvastatin calcium in a halogenated hydrocarbon such as methylene dichloride, chloroform, carbon tetrachloride or mixture thereof.
b) partial recovery of halogenated hydrocarbon & addition of anti-oxidant like butylated hydroxyanisole, butylated hydroxy toluene or propyl gallate etc.
c) lowering of temperature of organic layer to 10-20 °C.
d) addition of an aliphatic ether as anti-solvent for crystallization of material.
e) further stirring for complete crystallization of material at 10-20 °C.
f) isolation of material by filtration followed by drying at 50-60 °C for 30-40 hours to get amorphous Rosuvastatin calcium as confirmed by XRD pattern in figure II.

[0029] According to yet another aspect of the present invention, the aliphatic ether used is selected from Diisopropyl-ether, methyl tert butyl ether, dimethyl ether, diethyl ether or mixture thereof.

[0030] According to another exemplary process, which does not correspond to the invention as defined in the claims, but it is useful for the understanding of the claimed processes thereof, for preparation of stable amorphous Rosuvastatin Calcium which comprises:

a) dissolution of any crystalline form of Rosuvastatin calcium in a aliphatic ketone.
b) partial recovery of the aliphatic ketone & addition of anti-oxidant like butylated hydroxyanisole, butylated hydroxytoluene or propyl gallate etc.
c) lowering of temperature of organic layer to 10-20 °C.
d) addition of an aliphatic ether as antisolvent for crystallization of material.
e) further stirring for complete crystallization of material at 10-20 °C.
f) isolation of material by filtration followed by drying at 50-60 °C for 30-40 hours to get amorphous Rosuvastatin calcium as confirmed by XRD pattern in figure II

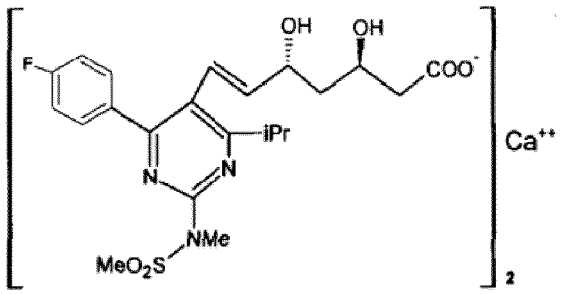
[0031] According to another aspect the aliphatic ketone used is selected from acetone, ethyl methyl ketone, diethyl ketone, dimethyl ketone, dipropyl ketone, dibutyl ketone or mixture thereof and aliphatic ether used is selected from Diisopropylether, methyl tert butyl ether, dimethyl ether, diethyl ether or mixture thereof.

[0032] According to another exemplary process, which does not correspond to the invention as defined in the claims, but it is useful for the understanding of the claimed processes thereof, for preparation of amorphous Rosuvastatin Calcium which comprises:

a) stirring of crystalline form M of Rosuvastatin calcium in a water.
b) Addition of sodium hydroxide solution & heating the reaction mass to 35-40°C.
c) Stirring for 30-60 minutes.
d) Washing with aliphatic ether followed by layer separation.
e) pH of aqueous layer containing product is adjusted to 8.5-9.5 at 25-30 °C.
f) addition of calcium chloride solution in water.
g) Stirring to ensure complete crystallization,
h) Drying at 50-60 °C for 10-15 hours.
i) Slurry washing of dried material in aliphatic ether containing anti-oxidant/ stabilizer like butylated hydroxyanisole or butylated hydroxytoluene etc.
j) Re-filtered material & dried wet cake at 50-60 °C to get stable amorphous Rosuvastatin calcium as confirmed by XRD pattern in figure II.

Claims

1. A process for the preparation of highly pure crystalline form 'M' of the compound 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt designated as form "M" of Rosuvastatin calcium of formula I or hydrates thereof:



Formula I

wherein the polymorphic crystalline form M of Rosuvastatin Calcium has characteristic peaks as given below:

2- Theta	Relative intensity (%) (Peaks having > 40% Intensity are mentioned)
6.83	63
8.14	49
9.15	73

(continued)

2- Theta	Relative intensity (%) (Peaks having > 40% Intensity are mentioned)
10.23	43
11.30	95
15.60	42
17.82	48
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19.44	68
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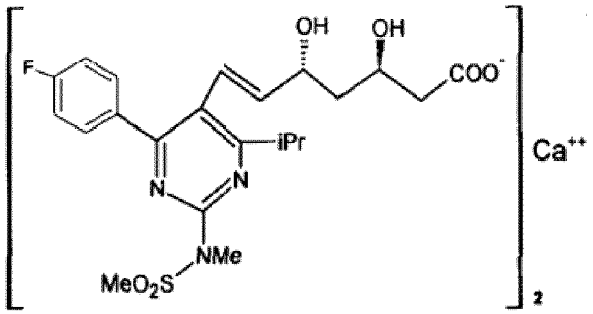
20.82	80
22.01	65
22.85	74
24.14	56
24.56	40

which comprises:

i. Deprotection of tert-butyl-2-((4R,6S)-6-((E)-2-(4(-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulphonamido)pyrimidin-5-yl)vinyl)-2,2- dimethyl-1,3-dioxan-4-yl) acetate in acetonitrile using dilute hydrochloric acid.
ii. Hydrolysis of resulting material with aqueous Caustic solution.
iii. Complete removal of acetonitrile from reaction mass under vacuum.
iv. Addition of water & methyl tert-butyl ether.
v. Layer separation.
vi. Isolation of Rosuvastatin calcium by addition of calcium chloride to aqueous layer.
vii. Recrystallization of resulting Rosuvastatin Calcium (wet or dry) by dissolving the product using an aliphatic ketone such as acetone, ethyl methyl ketone, diethyl ketone, dipropyl ketone, dibutyl ketone or mixture thereof & recrystallization by adding water as anti-solvent.
viii. Isolation of novel Rosuvastatin calcium crystalline form M by routine filtration & drying;

wherein the anti-isomer content is very low (<0.1% by HPLC) or even 'Not Detected'.

2. A process for the preparation of highly pure crystalline form 'M' of the compound 7-[4-(4-flurophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-enoic acid Calcium salt designated as form "M" of Rosuvastatin calcium of formula I or hydrates thereof:



Formula I

wherein the polymorphic crystalline form M of Rosuvastatin Calcium has characteristic peaks as given below:

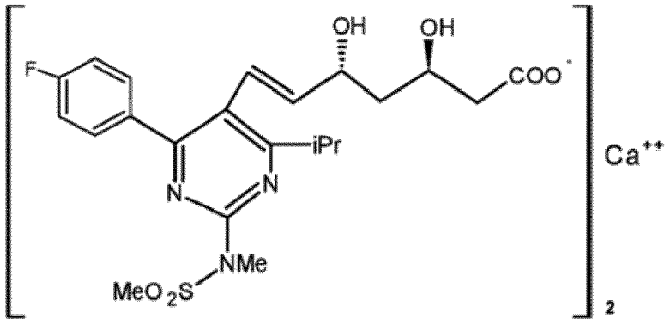
2- Theta	Relative intensity (%) (Peaks having > 40% Intensity are mentioned)
6.83	63
8.14	49
9.15	73
10.23	43
11.30	95
15.60	42
17.82	48
19.17	100
19.44	68
20.30	80
20.82	80
22.01	65
22.85	74
24.14	56
24.56	40

which comprises:

step vii of claim 1,
wherein the ratio of aliphatic ketone & water can be selected from 10:5, 5:5 or even 3:8.

Patentansprüche

1. Verfahren zur Herstellung der hochreinen kristallinen Form "M" der Verbindung 7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-Dihydroxy-hept-6-ensäure Calciumsalz, bezeichnet als Form "M" von Rosuvastatin-Calcium der Formel I oder Hydrate davon:



Formel 1

wobei die polymorphe kristalline Form M von Rosuvastatin-Calcium charakteristische Peaks wie unten angegeben aufweist:

2-Theta	Relative Intensität (%) (Peaks mit > 40 % Intensität werden erwähnt)
6,83	63

(fortgesetzt)

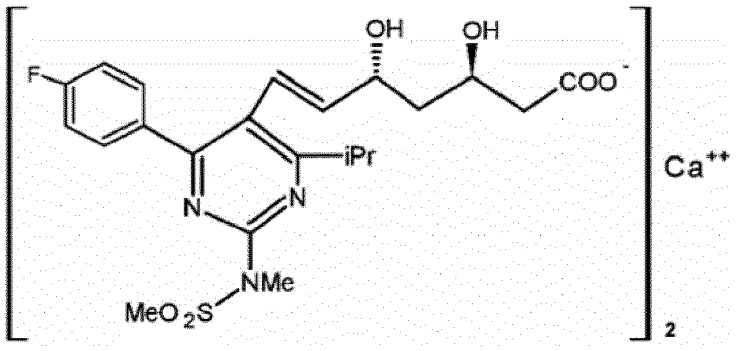
2-Theta	Relative Intensität (%) (Peaks mit > 40 % Intensität werden erwähnt)
8,14	49
9,15	73
10,23	43
11,30	95
15,60	42
17,82	48
19,17	100
19,44	68
20,30	80
20,82	80
22.01	65
22,85	74
24,14	56
24,56	40

das umfasst:

i. Entschützung von tert.-Butyl-2-((4R,6S)-6-((E)-2-(4(-(4-fluorphenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)Vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetat in Acetonitril mit verdünnter Salzsäure.
ii. Hydrolyse des resultierenden Materials mit wässriger Ätzlösung.
iii. Vollständige Entfernung von Acetonitril aus der Reaktionsmasse unter Vakuum.
iv. Zugabe von Wasser & Methyl-tert.-butylether.
v. Schichttrennung.
vi. Isolierung von Rosuvastatin-Calcium durch Zugabe von Calciumchlorid zur wässrigen Schicht.
vii. Umkristallisation des resultierenden Rosuvastatin-Calciums (nass oder trocken) durch Auflösen des Produkts unter Verwendung eines aliphatischen Ketons wie Aceton, Ethylmethylketon, Diethylketon, Dipropylketon, Dibutylketon oder einer Mischung davon und Umkristallisation durch Zugabe von Wasser als Anti-Lösungsmittel.
viii. Isolierung der neuen kristallinen Form M von Rosuvastatin-Calcium durch Routinefiltration und -trocknung;

wobei der Anti-Isomer-Gehalt sehr gering ist (< 0,1 % laut HPLC) oder sogar "nicht nachgewiesen".

2. Verfahren zur Herstellung der hochreinen kristallinen Form "M" der Verbindung 7-[4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R,5S)-Dihydroxy-hept-6-ensäure Calciumsalz, bezeichnet als Form "M" von Rosuvastatin-Calcium der Formel I oder Hydrate davon:



Formel 1

wobei die polymorphe kristalline Form M von Rosuvastatin-Calcium charakteristische Peaks wie unten angegeben aufweist:

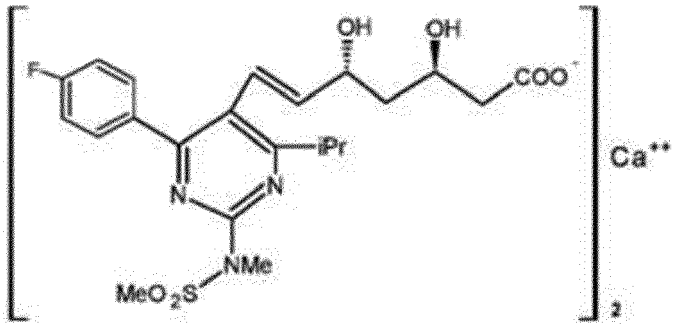
2-Theta	Relative Intensität (%) (Peaks mit > 40 % Intensität werden erwähnt)
6,83	63
8,14	49
9,15	73
10,23	43
11,30	95
15,60	42
17,82	48
19,17	100
19,44	68
20,30	80
20,82	80
22.01	65
22,85	74
24,14	56
24,56	40

das umfasst:

Schritt vii von Anspruch 1,
wobei das Verhältnis von aliphatischem Keton & Wasser aus 10:5, 5:5 oder sogar 3:8 ausgewählt werden kann.

Revendications

1. Procédé de préparation de la forme cristalline hautement pure 'M' du composé de l'acide 7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonyl-amino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-hept-6-énoïque Sel de calcium désigné sous la forme "M" de la Rosuvastatine calcique de formule I ou ses hydrates:



Formule I

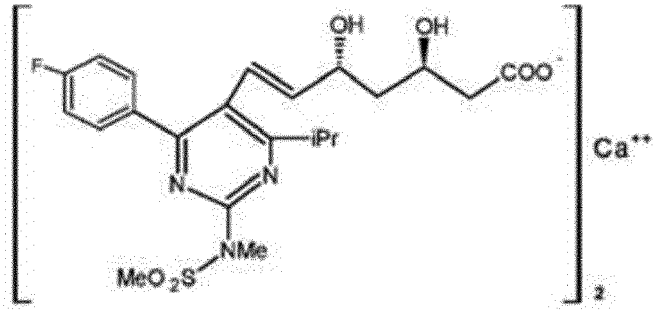
dans laquelle la forme cristalline polymorphe M de la Rosuvastatine calcique a des pics caractéristiques comme indiqué ci-dessous:

2-Théta	Intensité relative (%) (Les pics ayant > 40 % d'intensité sont mentionnés)
6,83	63
8,14	49
9,15	73
10,23	43
11,30	95
15,60	42
17,82	48
19,17	100
19,44	68
20,30	80
20,82	80
22.01	65
22,85	74
24,14	56
24,56	40

qui comprend:

i. Déprotection du tert-butyl-2-((4R,6S)-6-((E)-2-(4(-(4-fluorophényl)-6-isopropyl-2-(N-méthylméthylsulfonamido) pyrimidin-5-yl) vinyle)-2,2-diméthyl-1,3-dioxan-4-yl) acétate dans l'acétonitrile en utilisant de l'acide chlorhydrique dilué.
ii. Hydrolyse du matériau résultant avec une solution caustique aqueuse.
iii. Élimination complète de l'acétonitrile de la masse réactionnelle sous vide.
iv. Ajout d'eau et d'éther de méthyle et de tertio-butyle.
v. Séparation des couches.
vi. Isolement de la Rosuvastatine calcique par addition de chlorure de calcium à la couche aqueuse.
vii. Recristallisation de la Rosuvastatine calcique résultante (humide ou sèche) en dissolvant le produit à l'aide d'une cétone aliphatique telle que l'acétone, l'éthylméthylcétone, la diéthylcétone, le dipropylcétone, dibutylcétone ou leur mélange & recristallisation par ajout d'eau comme anti-solvant.
viii. Isolement de la nouvelle forme cristalline M de Rosuvastatine calcique par filtration et séchage de routine; dans laquelle la teneur en anti-isomères est très faible (<0,1 % par HPLC) ou même « Non Détectée ».

2. Procédé de préparation de la forme cristalline hautement pure 'M' du composé de l'acide 7-[4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthylsulfonylamino)-pyrimidin-5-yl]-(3R, 5S)-dihydroxy-hept-6-énoïque Sel de calcium désigné sous la forme "M" de la Rosuvastatine calcique de formule I ou ses hydrates:



Formule I

dans laquelle la forme cristalline polymorphe M de la Rosuvastatine calcique a des pics caractéristiques comme indiqué ci-dessous:

2-Théta	Intensité relative (%) (Les pics ayant > 40 % d'intensité sont mentionnés)
6,83	63
8,14	49
9,15	73
10,23	43
11,30	95
15,60	42
17,82	48
19,17	100
19,44	68
20,30	80
20,82	80
22.01	65
22,85	74
24,14	56
24,56	40

qui comprend:

étape vii de la revendication 1,
dans lequel le rapport de la cétone aliphatique et de l'eau peut être choisi parmi 10:5, 5:5 ou même 3:8.

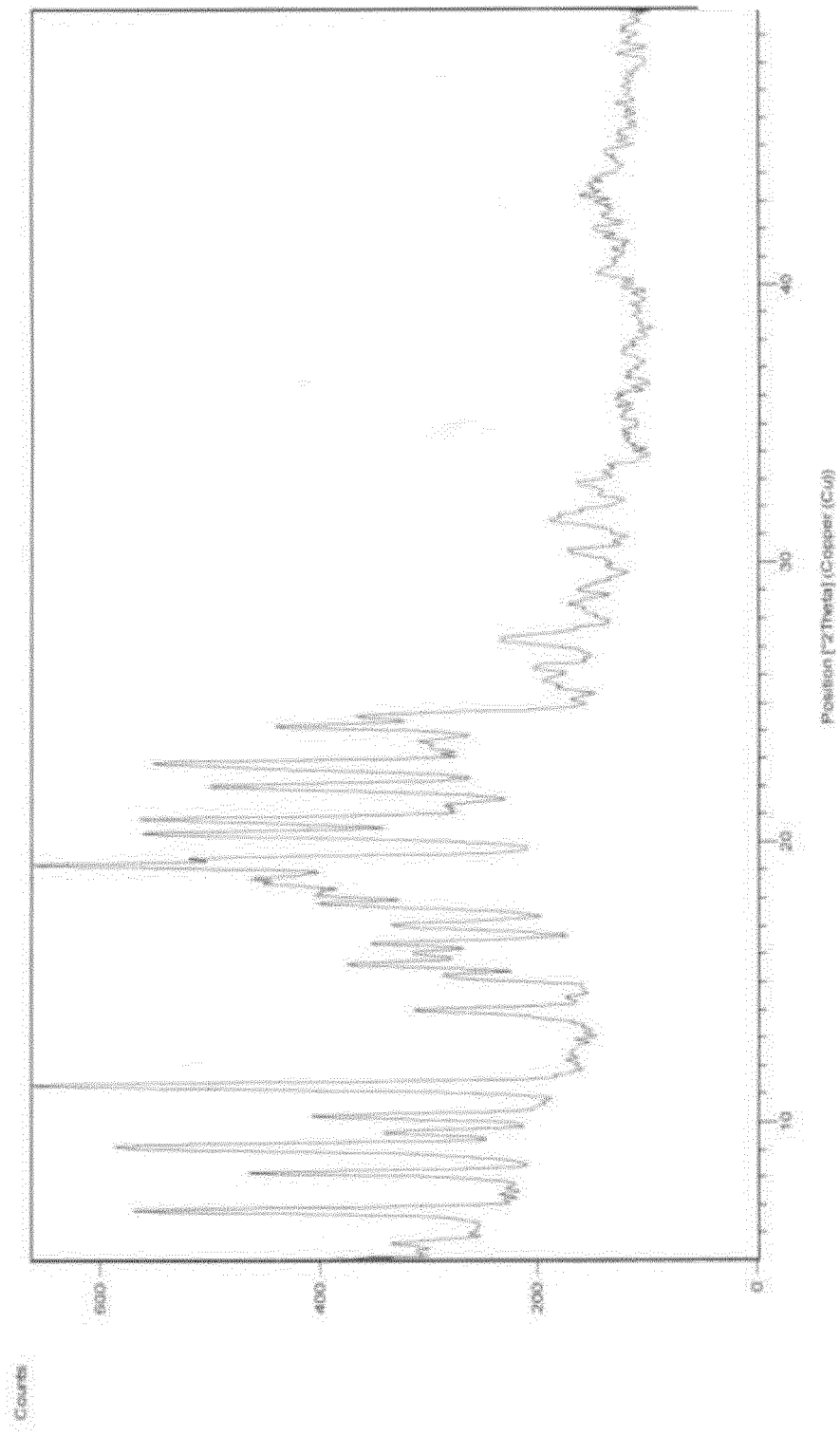


FIGURE I (Form M, Ratio 10:5 of Acetone:water)

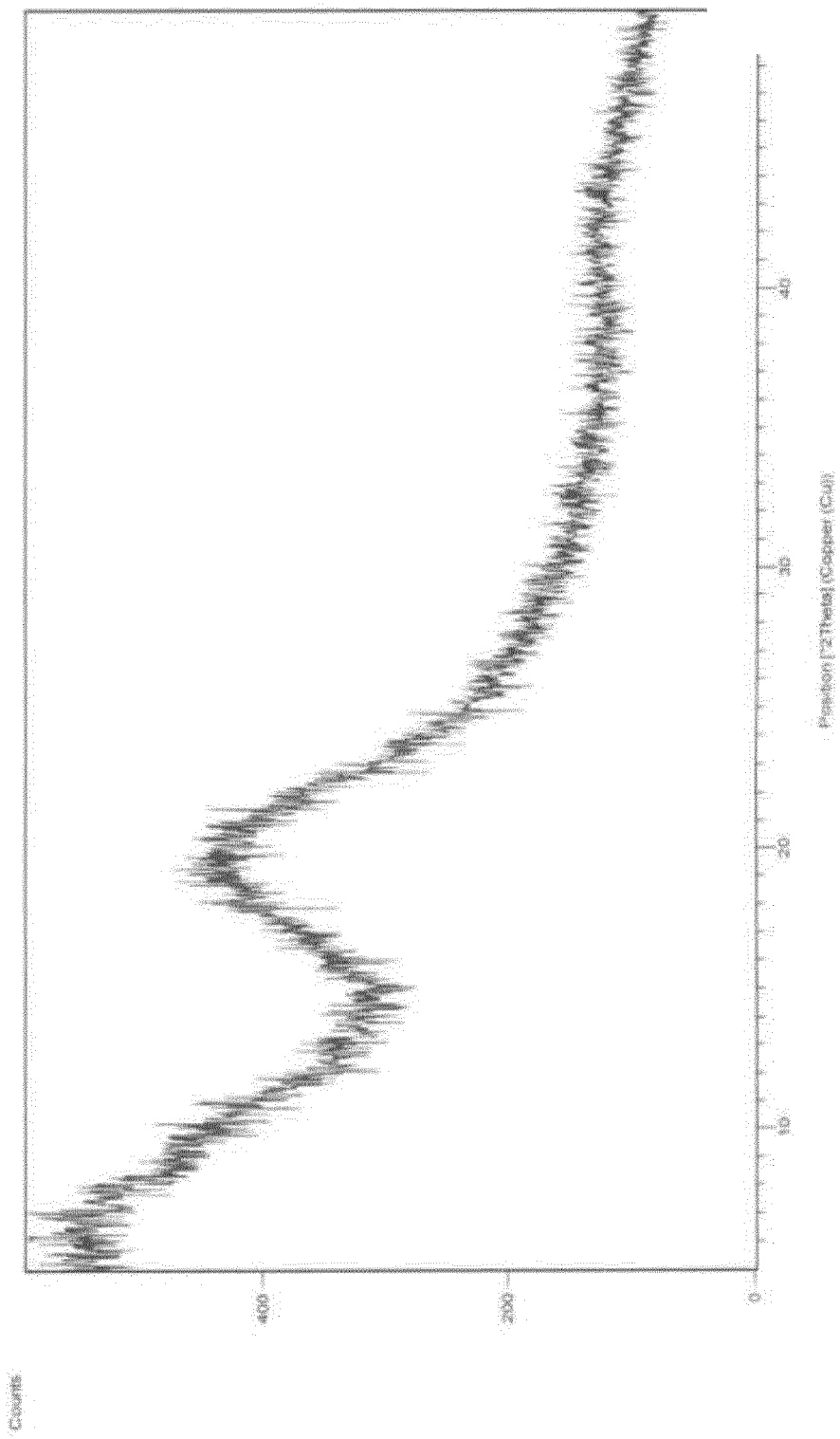


FIGURE II (Amorphous)

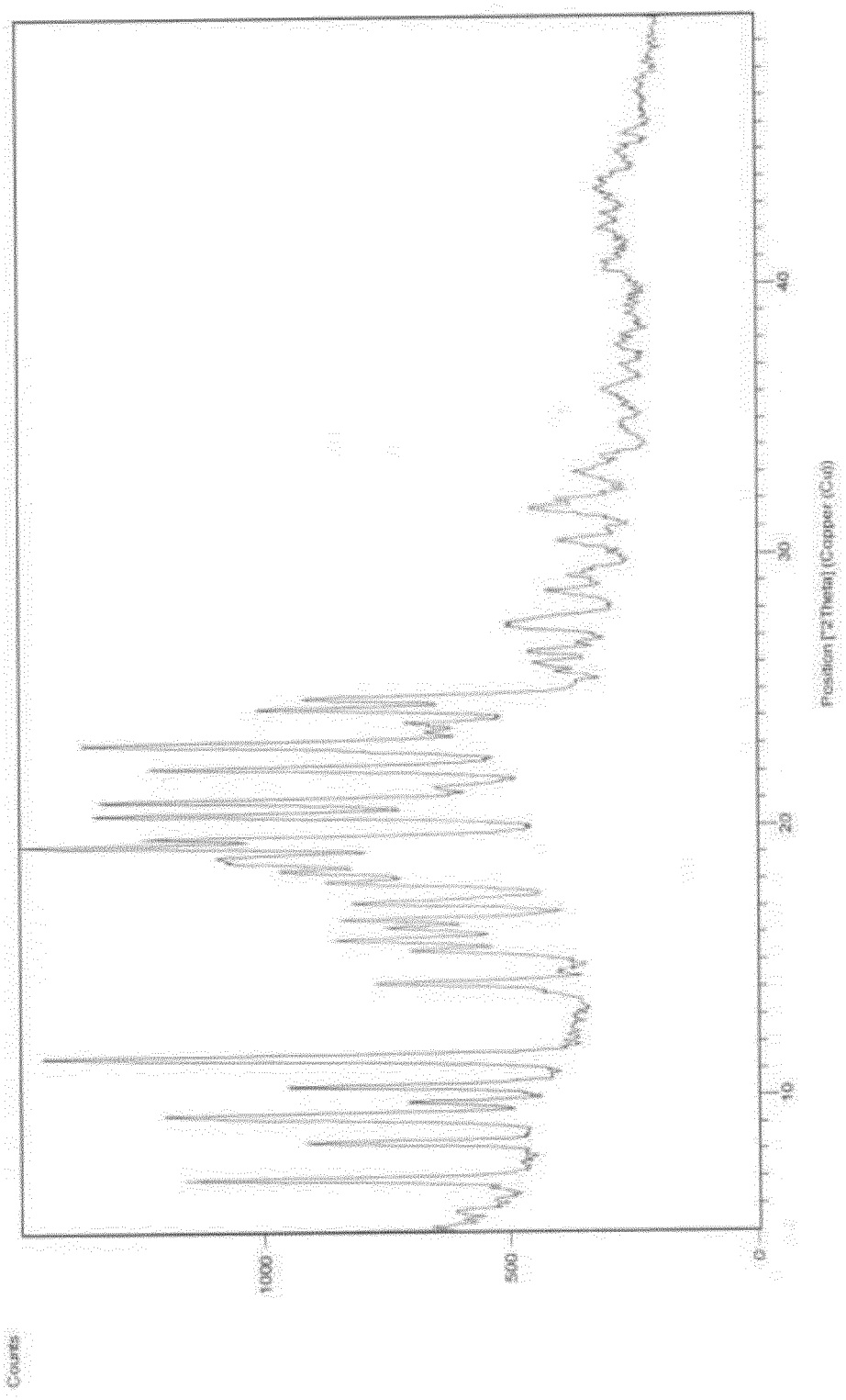


FIGURE III (FORM M, Ratio 5:5 of Acetone:water)

REFERENCES CITED IN THE DESCRIPTION

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- EP 0521471 A1 **[0005]**
- US 6777552 B **[0006]**
- WO 0042024 A **[0007]**
- WO 2005023779 A **[0008]**
- US 20080194604 A **[0008] [0009]**