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DESCRIPTION

SOLID PREPARATION COMPRISING NPY5 RECEPTOR ANTAGONIST

[Technical field]

[0001]

The present invention relates to a preparation for improving solubility of an NPY5 receptor antagonist in water. In particular, the present invention relates to a solid preparation of trans-N-(5-trifluoromethyl pyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide containing carboxymethylethylcellulose as an amorphous stabilizer.

[Background art]

[0002]

Neuropeptide Y (hereinafter, referred to as NPY) is a peptide consisting of 36 amino acid residues, and was isolated from porcine brain in 1982. NPY is widely distributed in the central nervous system and peripheral tissues of humans and animals.

It has been reported that NPY possesses a stimulating activity of food intake, an anti-seizure activity, a learning-promoting activity, an anti-anxiety activity, an anti-stress activity etc. in the central nervous system, and it may be pivotally involved in the central nervous system diseases such as depression, Alzheimer's disease and Parkinson's disease. NPY is thought to be associated with the cardiovascular diseases, since it induces a contraction of smooth muscles such as blood vessels or cardiac muscles in the peripheral tissues. Furthermore, NPY is also known to be



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involved in the metabolic diseases such as obesity, diabetes, and hormone abnormalities (Trends in Pharmacological Sciences, Vol.15, and 153 (1994)). Therefore, an NPY receptor antagonist is expected as a medicine for preventing or treating various diseases involved in the NPY receptor.

Subtypes: Y1, Y2, Y3, Y4, Y5, and Y6 have been identified as the NPY receptor (Trends in Pharmacological Sciences, Vol.18, and 372 (1997)). It has been suggested that the Y5 receptor is at least involved in the feeding behavior and its antagonist is expected as an anti-obestic agent (Peptides, Vol.18, and 445 (1997)).

[0003]

As this NPYY5 receptor antagonist, compounds described in International Publication Pamphlet WO 01/37826 and WO 03/076374 are exemplified and, particularly, trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide exhibits high anti-obesity effect. The present drug is orally administered and, according to study by the present inventors, it has been revealed that since the drug has low solubility in water, and it is not sufficiently dissolved in a digestive tract, an absorption amount is reduced. Since by such a drug, as a dose is increased, an absorption fraction is reduced, and an absorption rate easily varies due to digestion working at ingestion (mechanical stimulation due to constriction motion of a digestive tract, increase in a secretion amount of a digestive fluid, prolongation of a digestive tract retention time and the like) as compared with at hunger, an expected therapeutic effect is not obtained, or an occasional harmful effect is caused in some cases. For this reason, particularly, increase in a rate of dissolution of a drug from a solid

preparation is important for developing an oral preparation.

[0004]

As one of means for improving solubility of a poorly water-soluble drug in a solid preparation in water, a solid dispersion in which a drug molecule is uniformly dispersed in a base of the solid state, and a drug molecule is in the state where it does not form a crystal (amorphous) is used. As such a solid dispersion, a preparation containing a drug, an amorphous stabilizer and an amorphousization inducing agent is being studied. For example, Patent Document 1 discloses a solid dispersion obtained by heating or mechanochemically treating a preparation containing nicardipine hydrochloride, 15% by weight of urea as an amorphousization inducing agent, and hydroxypropylmethylcellulose as an amorphousization stabilizer. In addition, Patent Document 2 discloses a solid dispersion obtained by heating or mechanochemically treating a preparation containing efonidipine hydrochloride, 11% by weight of urea as an amorphousization inducing agent, and hydroxypropylmethylcellulose acetate succinate as an amorphous stabilizer. Further, Non-patent Document 1 discloses a solid dispersion containing nifedipine, polyvinylpyrrolidone and 7% by weight of urea.

[0005]

However, solid dispersions of Patent Documents 1 and 2 are such that a production process is a method of giving a burden excessive for a drug, such as high temperature heating and mechanochemical treatment and, therefore, there is a possibility of degradation of a drug. In addition, increase of solubility of drugs in water are described; efonidipine hydrochloride in Patent Document 3, cyclosporine A in Patent Document 4,

bicalutamide in Patent Document 5, amifostine in Patent Document 6, itraconazole in Patent Document 7, 6-hydroxy-5,7-dimethyl-2-methylamino-4-(3-pyridylmethyl) benzothiazol in Patent Document 8, nifedipine in Non-patent Document 1, 4"-o-(4-methoxyphenyl) acetyltyrosine in Non-patent Document 2. However, each optimal kind and amount of an amorphous stabilizer and amorphosization inducing agent depends on a kind of drug. In addition, though Patent Document 9 describes a solid dispersion containing a poorly water-soluble drug, a preparation of a NPY5 receptor antagonist blended in the present preparation is not specifically described.

On the other hand, though a patent application of a solid preparation of an NPY5 receptor antagonist has been filed, carboxymethylethylcellulose is not used therein (PCT/JP2008/066818).

[Prior art]

[Patent Document]

[0006]

[Patent Document 1] International Publication WO 97/06781

[Patent Document 2] Japanese Patent Publication No.H9-309834

[Patent Document 3] Japanese Patent Publication No.H2-49728

[Patent Document 4] Japanese Patent Publication No.2004-528358

[Patent Document 5] Japanese Patent Publication No.2004-143185

[Patent Document 6] Japanese Patent Publication No.2002-529519

[Patent Document 7] Japanese Patent Publication No.2004-67606

[Patent Document 8] Japanese Patent Publication No.H9-309828

[Patent Document 9] International Publication WO 2007/108463

[Non-Patent Document]

[0007]

[Non-Patent Document 1] 2005 Report of Important Study of Drug Design etc. Human Science Study, Third Field, Objective No. KH31024 (publication date: July 31, 2006)

[Non-Patent Document 2] Yakuzaigaku Vol.53, No.4, p.221-228

[Disclosure of the invention]

[Problems to be solved by the invention]

[0008]

Development of a novel solid preparation with improved solubility of an NPY₅ receptor antagonist, especially trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide, has been desired.

[Means to solve the problems]

[0009]

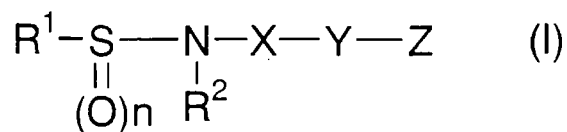
The present inventors intensively studied and found out that solubility of an NPY₅ receptor antagonist, particularly trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide, can be improved by containing carboxymethylethylcellulose (hereinafter, also referred to as CMEC), and an optional amorphousization inducing agent in a solid preparation of an NPY₅ receptor antagonist.

[0010]

The present invention relates to:

(1) a solid preparation comprising a compound represented by formula (I):

[Chemical formula 1]



[wherein,

R¹ is optionally substituted lower alkyl, optionally substituted cycloalkyl or optionally substituted aryl,

R² is hydrogen or lower alkyl, and

R¹ and R² taken together may form lower alkylene,

n is 1 or 2,

X is optionally substituted lower alkylene, optionally substituted lower alkenylene, optionally substituted -CO-lower alkylene, optionally substituted -CO-lower alkenylene or

[Chemical formula 2]



(wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen or lower alkyl, wherein

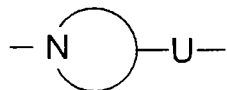
[Chemical formula 3]



is optionally substituted cycloalkylene, optionally substituted cycloalkenylene, optionally substituted bicycloalkylene, optionally substituted arylene or optionally substituted heterocyclediyl and p and q are each independently 0 or 1)

$\cdot\text{NR}^2\text{-X}\cdot$ is

[Chemical formula 4]



(wherein

[Chemical formula 5]



is piperidinediyl, piperazinediyl, pyridinediyl, pyrazinediyl, pyrrolidinediyl or pyrrolediyl, and U is a single bond, lower alkylene or lower alkenylene),

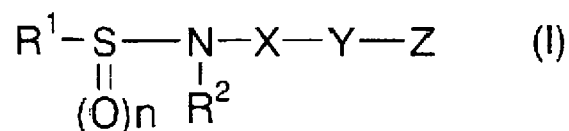
Y is OCONR^7 , CONR^7 , CSNR^7 , NR^7CO or NR^7CS ,

R^7 is hydrogen or lower alkyl,

Z is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted amino, optionally substituted lower alkoxy, optionally substituted carbocycle or optionally substituted heterocyclyl] or a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a solvate thereof, and carboxymethylethylcellulose,

(2) the solid preparation according to (1) comprising a compound represented by formula (I):

[Chemical formula 6]



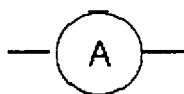
[wherein X is

[Chemical formula 7]



wherein

[Chemical formula 8]

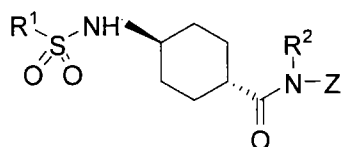


is heterocyclediyl, and R1 is optionally substituted C3 to C10 alkyl or optionally substituted C5 to C6 cycloalkyl, and the other symbols are the same as defined in (1)]

or a pharmaceutically acceptable salt thereof, or a solvate thereof, and carboxymethylethylcellulose,

(3) the solid preparation according to (1) comprising a compound

[Chemical formula 9]



[wherein, R1 is lower alkyl, R2 is hydrogen or lower alkyl, Z is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted amino, optionally substituted lower alkoxy, optionally substituted carbocyclyle or optionally substituted heterocyclyl]

or a pharmaceutically acceptable salt thereof, or a solvate thereof, and carboxymethylethylcellulose,

(4) the solid preparation according to any one of (1) to (3), wherein the

content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 5 to 50% by weight,

(5) the solid preparation according to (4), wherein the content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 15 to 30% by weight,

(6) the solid preparation according to (4), wherein the content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 25 to 30% by weight,

(7) the solid preparation according to any one of (1) to (6), wherein a compound represented by formula (I) is trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide,

(8) the solid preparation according to (7), which contains 5 to 50% by weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, and 50 to 95 % by weight of carboxymethylethylcellulose,

(9) the solid preparation according to (7), which contains 15 to 30% by weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, and 70 to 85% by weight of carboxymethylethylcellulose,

(10) the solid preparation according to (7), which contains 25 to 30% by weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, and 70 to 75% by weight of carboxymethylethylcellulose,

(11) the solid preparation according to any one of (1) to (10), wherein the

content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:1 to 1:19,

(12) the solid preparation according to (11), wherein the content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:2.33 to 1:5.67,

(13) the solid preparation according to (11), wherein the content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:2.33 to 1:3,

(14) the solid preparation according to any one of (1) to (13), which further contains an amorphousization inducing agent,

(15) the solid preparation according to (14), wherein the amorphousization inducing agent is 1, 2 or more selected from the group consisting of amino acid or a salt thereof, aspartame, erythorbic acid or a salt thereof, ascorbic acid or a salt thereof, stearic acid ester, aminoethylsulfonic acid, inositol, ethylurea, citric acid or a salt thereof, glycyrrhizic acid or a salt thereof, gluconic acid or a salt thereof, creatinine, salicylic acid or a salt thereof, tartaric acid or a salt thereof, succinic acid or a salt thereof, calcium acetate, saccharine sodium, aluminum hydroxide, sorbic acid or a salt thereof, dehydroacetic acid or a salt thereof, sodium thiomalate, nicotinic acid amide, urea, fumaric acid or a salt thereof, macrogols, maltose, maltol, mannitol, meglumine, sodium desoxycholate and phosphatidylcholine,

(16) the solid preparation according to (14), wherein the amorphousization inducing agent is urea,

(17) the solid preparation according to any one of (14) to (16), wherein a

content of the amorphousization inducing agent in the preparation is less than 8% by weight,

(18) the solid preparation according to (17), wherein a content of the amorphousization inducing agent in the preparation is 0.1 to 6 % by weight,

(19) the solid preparation according to (17), wherein a content of the amorphousization inducing agent in the preparation is 2 to 4 % by weight,

(20) the solid preparation according to any one of (1) to (13), which does not contain the amorphousization inducing agent,

(21) the solid preparation according to any one of (1) to (20), which is a solid dispersion,

(22) the solid preparation according to any one of (1) to (21), which is produced by a spray drying method,

(23) a tablet containing the solid preparation according to any one of (1) to (22),

(24) the tablet according to (23), which has a weight of 450 to 550 mg per one tablet according to (23),

(25) a process for producing the solid preparation according to (22), using a spray drying method,

(26) a method of improving the solubility of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide, comprising adding carboxymethylethylcellulose to a solid preparation containing trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide ,

(27) the method of improving the solubility of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide,

comprising adding an amorphousization inducing agent to a solid preparation containing trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide ,

(28) a method of controlling the release rate of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide as 60% or more after 60 minutes and 70% or more after 180 minutes in second fluid of the Japanese Pharmacopoeia, Dissolution Test.

[Effects of the invention]

[0011]

The solid preparation of the present invention can increase dissolution of the NPY₅ receptor antagonist, especially trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino)cyclohexanecarboxamide, from the preparation. In addition, preferably, the solid preparation can maintain the amorphous state for a long period of time. More preferably, the size of preparation (e.g., tablet) can be downsized to improve ease of dosing.

[Brief description of the drawings]

[0012]

[Fig.1] Dissolution concentration profile of S-2367 in the preparation containing CMEC.

[Fig.2] Dissolution rate profile of S-2367 in the preparation containing CMEC.

[Fig.3] An X-ray diffraction pattern of preparations containing CMEC just

after production.

[Fig.4] An X-ray diffraction pattern of preparations containing CMEC after preservation.

[Fig.5] Dissolution profile of the preparation containing CMEC and urea (S-2367 15% containing).

[Fig.6] Dissolution profile of the preparation containing CMEC and urea (S-2367 20% containing).

[Fig.7] An X-ray diffraction pattern of preparations containing CMEC and urea just after production.

[Fig.8] An X-ray diffraction pattern of preparations containing CMEC and urea after preservation.

[Best mode for carrying out the invention]

[0013]

The NPY₅ receptor antagonist used in the present invention is preferably a compound represented by the formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof, and is described in WO 01/37826 and WO 03/076374 International Publication Pamphlet.

[0014]

Herein, "halogen" includes fluorine, chlorine, bromine and iodine. Particularly, fluorine and chlorine are preferable.

"Lower alkyl" includes straight or branched alkyl of a carbon number of 1 to 10, and examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl and n-decyl.

"Lower alkyl" in R^1 is preferably a carbon number of 3 to 10, further preferably a carbon number of 3 to 6, and most preferably isopropyl or t-butyl.

"Lower alkyl" in other cases is preferably a carbon number of 1 to 6, and further preferably a carbon number of 1 to 4.

Examples of a substituent of "lower alkyl optionally having a substituent" in Z include: (1) halogen; (2) cyano; and (3) (i) hydroxy, (ii) lower alkoxy, (iii) mercapto, (iv) lower alkylthio, (v) acyl, (vi) acyloxy, (vii) carboxy, (viii) lower alkoxycarbonyl, (ix) imino, (x) carbamoyl, (xi) thiocarbamoyl, (xii) lower alkylcarbamoyl (xiii) lower alkylthiocarbamoyl, (xiv) amino, (xv) lower alkylamino or (xvi) heterocyclic carbonyl, each optionally being substituted with one or more replaceable groups selected from a substituent group β defined below.

Examples of a substituent of "lower alkyl optionally having a substituent" in the case other than Z (e.g., the case in R^1) include one or more groups selected from a substituent group β , and an arbitrary position may be substituted with these substituents.

The substituent group β is a group consisting of halogen, optionally protected hydroxyl, mercapto, lower alkoxy, lower alkenyl, amino, lower alkylamino, lower alkoxycarbonylamino, lower alkylthio, acyl, carboxy, lower alkoxycarbonyl, carbamoyl, cyano, cycloalkyl, phenyl, phenoxy, lower alkylphenyl, lower alkoxyphenyl, halogenophenyl, naphthyl and a heterocyclic group.

A lower alkyl part of "lower alkoxy," "lower alkoxycarbonyl," "lower alkoxycarbonyl lower alkyl," "lower alkylphenyl," "lower alkoxyphenyl,"

“lower alkylcarbamoyl,” “lower alkylthiocarbamoyl,” “lower alkylamino,” “halogeno lower alkyl,” “hydroxy lower alkyl,” “phenyl lower alkoxy,” “lower alkylthio,” “phenyl lower alkylthio,” “lower alkoxycarbonylamino,” “lower alkoxycarbonyl lower alkenyl,” “lower alkylsulfinyl,” “lower alkylsufonyl,” “aryl lower alkoxycarbonyl,” “lower alkylbenzoyl” and “lower alkoxybenzoyl” is the same as the “lower alkyl.”

Examples of a substituent of “lower alkoxy optionally having a substituent” include one or more groups selected from a substituent group β , preferably phenyl, lower alkylphenyl, lower alkoxyphenyl, naphthyl or a heterocyclic group.

“Cycloalkyl” includes cyclic alkyl of a carbon number of 3 to 8, and preferably 5 or 6. Specifically, examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Examples of a substituent of “cycloalkyl optionally having a substituent” include one or more groups selected from a substituent group α , and any position may be substituted.

“Bicycloalkyl” includes a group obtained by removing one hydrogen from an aliphatic ring of a carbon number of 5 to 8 in which two rings share two or more atoms. Specifically, examples include bicyclo[2.1.0]pentyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and bicyclo[3.2.1]octyl.

“Lower alkenyl” includes straight or branched alkenyl of a carbon number of 2 to 10, preferably a carbon number of 2 to 8, and further preferably a carbon number of 3 to 6, and having one or more double bonds at an arbitrary position. Specifically, examples include vinyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl,

pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl and decenyl.

A "lower alkenyl" part in "lower alkoxy carbonyl lower alkenyl" is the same as the "lower alkenyl."

Examples of a substituent of "lower alkenyl optionally having a substituent" include halogen, lower alkoxy, lower alkenyl, amino, lower alkylamino, lower alkoxy carbonylamino, lower alkylthio, acyl, carboxy, lower alkoxy carbonyl, carbamoyl, cyano, cycloalkyl, phenyl, lower alkylphenyl, lower alkoxyphenyl, naphthyl and/or a heterocyclic group.

"Acyl" includes (1) straight or branched alkylcarbonyl or alkenylcarbonyl of a carbon number of 1 to 10, further preferably a carbon number of 1 to 6, most preferably a carbon number of 1 to 4, (2) cycloalkylcarbonyl of a carbon number of 4 to 9, preferably a carbon number of 4 to 7, and (3) arylcarbonyl of a carbon number of 7 to 11. Specifically, examples include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, pivaloyl, hexanoyl, acryloyl, propioyl, methacryloyl, crotonoyl, cyclopropylcarbonyl, cyclohexylcarbonyl, cyclooctylcarbonyl and benzoyl.

An acyl part of "acyloxy" is as defined above.

"Cycloalkenyl" includes an entity having 1 or more double bonds at an arbitrary position in the cycloalkyl ring and, specifically, examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cyclohexadienyl.

Examples of the substituent of "cycloalkenyl optionally having a substituent" include one or more groups selected from a substituent group β .

Examples of a substituent of "amino optionally having a substituent"

include a substituent group β , benzoyl optionally having a substituent and/or heterocyclic carbonyl optionally having a substituent (herein, the substituent is hydroxy, lower alkyl, lower alkoxy and/or lower alkylthio.)

"Aryl" is a monocyclic or polycyclic aromatic carbocyclic group, and includes phenyl, naphthyl, anthryl and phenanthryl. In addition, the aryl also includes aryl condensed with other non-aromatic hydrocarbon cyclic group and, specifically, examples include indanyl, indenyl, biphenyl, acenaphthyl, tetrahydronaphthyl and fluorenyl. Particularly, phenyl is preferable.

An aryl part of "aryl lower alkoxy carbonyl" is the same.

"Aryl optionally having a substituent" and "phenyl optionally having a substituent" in Z include "aryl" or "phenyl" optionally substituted with a substituent group α , lower alkyl optionally substituted with one or more replaceable groups selected from a substituent group α , or the like.

Examples of a substituent of "aryl optionally having a substituent" and "phenyl optionally having a substituent" other than Z include one or more groups selected from a substituent group β .

"Hydrocarbon cyclic group" includes the "cycloalkyl," the "cycloalkenyl," the "bicycloalkyl" and the "aryl."

"Non-aromatic hydrocarbon cyclic group" includes the "cycloalkyl," the "cycloalkenyl" and the "bicycloalkyl."

"Hydrocarbon cyclic group optionally having a substituent" includes the "cycloalkyl optionally having a substituent," the "cycloalkenyl optionally having a substituent," the "bicycloalkyl optionally having a substituent" and the "aryl optionally having a substituent."

“Heterocyclic group” includes a heterocycle having one or more heteroatoms arbitrarily selected from O, S and N in a ring and, specifically, examples include 5- to 6-membered heteroaryls such as pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, furyl and thienyl; bicyclic condensed heterocyclic groups such as indolyl, isoindolyl, indazolyl, indoliziny, indolinyl, isoindolinyl, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzopyranyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, quinazolinyl, quinolyl, isoquinolyl, naphthyridinyl, dihydropyridyl, tetrahydroquinolyl, tetrahydrobenzothienyl and the like; tricyclic condensed heterocyclic groups such as carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxadiny, dibenzofuryl and the like; non-aromatic heterocyclic groups such as dioxanyl, thiiranyl, oxiranyl, oxathiolanyl, azetidiny, thianyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperidyl, pyrazinyl, morpholiny, morpholino, thiomorpholiny, thiomorpholino, dihydropyridyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolyl, tetrahydroisothiazolyl and the like.

A condensed heterocyclic group condensed with a ring other than a heterocycle (e.g., benzothiazolyl and the like) may have a bond on any ring.

A substituent of “heterocyclic group optionally having a substituent”

is the same substituent as that of "aryl optionally having a substituent."

A heterocyclic group part of "heterocyclic carbonyl," "heterocyclic oxy," "heterocyclic thio" and "heterocyclic substituted phenyl" is the same as the "heterocyclic group."

"Lower alkylene" includes a divalent group in which 1 to 6, preferably 2 to 6, further preferably 3 to 6 methylenes are continuous and, specifically, examples include methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene. Particularly preferable is tetramethylene.

A lower alkylene part of "lower alkylenedioxy" is the same as the "lower alkylene," preferably methylenedioxy or ethylenedioxy.

"Lower alkenylene" includes a divalent group in which 2 to 6, preferably 3 to 6, further preferably 4 to 5 methylenes are continuous, and at least one carbon-carbon bond is a double bond.

"Cycloalkylene" is a divalent group obtained by removing one hydrogen atom from the "cycloalkyl." In "cycloalkylene" in X, 1,4-cyclohexanediyl is preferable.

"Cycloalkenylene" includes a group having at least one double bond in a ring of the cycloalkylene.

"Bicycloalkylene" includes a group obtained by further removing one hydrogen from the "bicycloalkyl." Specifically, examples include bicyclo[2.1.0]pentylene, bicyclo[2.2.1]heptylene, bicyclo[2.2.2]octylene, bicyclo[3.2.1]octylene and the like.

"Heterocyclic diyl" includes a divalent group obtained by removing one hydrogen atom from the "heterocyclic group." Preferable are

piperidinediyl, piperazinediyl, pyridinediyl, pyrimidinediyl, pyrazinediyl, pyrrolidinediyl, or pyrrolediyl, more preferable is piperidinediyl.

“Arylene” includes a divalent group obtained by removing one hydrogen atom from the “aryl.” Preferable is phenylene.

“Heteroarylene” includes an entity having aromatic property among the “heterocyclic diyl.” Specifically, examples include pyrrolediyl, imidazolediyl, pyrazolediyl, pyridinediyl, pyridazinediyl, pyrimidinediyl, pyrazinediyl, triazolediyl, triazinediyl, isoxazolediyl, oxazolediyl, oxadiazolelediyl, isothiazolelediyl, thiazolelediyl, thiadiazolelediyl, furandiyl and thiophenediyl.

Examples of a substituent of “lower alkylene optionally having a substituent,” “lower alkenylene optionally having a substituent,” “cycloalkylene optionally having a substituent,” “cyclohexylene optionally having a substituent,” “bicycloalkylene optionally having a substituent,” “cycloalkenylene optionally having a substituent,” “phenylene optionally having a substituent,” “heterocyclic diyl optionally having a substituent” and “piperidinylene optionally having a substituent” include one or more replaceable groups selected from a substituent group β , preferably halogen, hydroxy, lower alkyl, halogeno lower alkyl, lower alkoxy, amino, lower alkylamino, acyl, carboxy or lower alkoxycarbonyl. An arbitrary position may be substituted with these groups.

Examples of the “pharmaceutically acceptable salt” include salts of inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid or phosphoric acid; salts of organic acids such as paratoluenesulfonic acid, methanesulfonic acid, oxalic acid or citric acid; salts of organic bases such as

ammonium, trimethylammonium or triethylammonium; salts of alkali metals such as sodium or potassium; and salts of alkaline earth metals such as calcium or magnesium.

A preferable solvate is a hydrate, and one molecule of the compound of the present invention may be coordinated with an arbitrary number of water molecules.

A prodrug is a derivative of the compound of the present invention having a group which can be chemically or metabolically degraded, and is a compound which serves as a pharmaceutically active compound of the present invention in vivo by solvolysis, or under physiological condition. A method of selecting a suitable prodrug derivative and a process for producing a suitable prodrug derivative are described, for example, in *Design of Prodrugs*, Elsevier, Amsterdam 1985.

For example, when the compound (I) of the present invention has carboxy, a prodrug such as an ester derivative produced by reacting carboxy of the compound (I) and a suitable alcohol, and an amide derivative produced by reacting carboxy of the compound (I) and a suitable amine is exemplified.

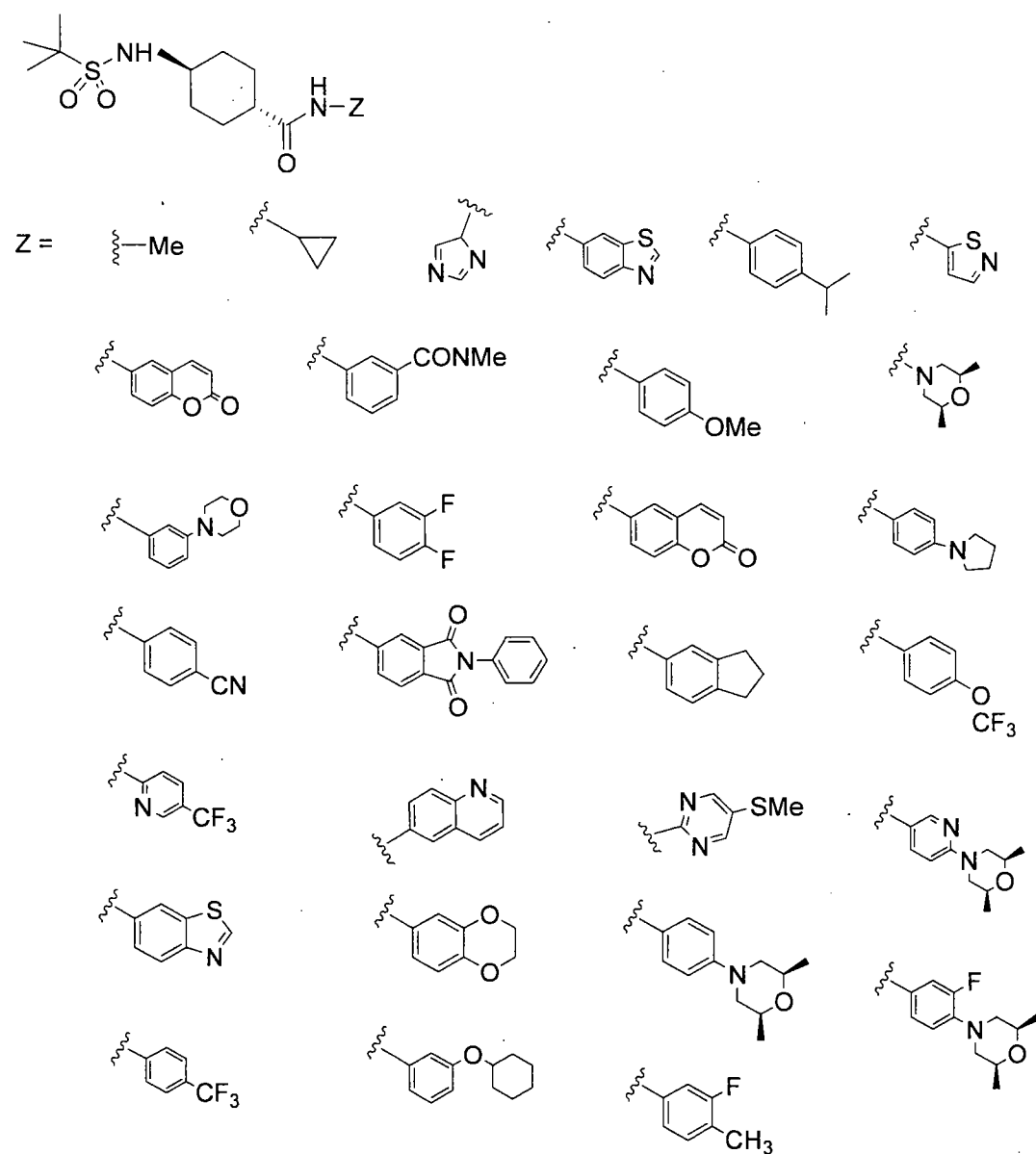
For example, when the compound (I) of the present invention has hydroxy, a prodrug such as an acyloxy derivative produced by reacting hydroxy of the compound (I) and suitable acyl halide or suitable acid anhydride is exemplified.

For example, when the compound (I) of the present invention has amino, a prodrug such as an amide derivative produced by reacting amino of the compound (I) and suitable acid halide or suitable mixed acid anhydride is exemplified.

When the compound (I) of the present invention has an asymmetric carbon atom, racemate, enantiomeric pairs and all steric isomers (geometrical isomer, epimer, enantiomer and the like) are included. In addition, when the compound (I) of the present invention has a double bond, and an E isomer and a Z isomer can be present, both of them are included. In addition, when X is cycloalkylene, both a cis isomer and a trans isomer are included.

Examples of the compound represented by the formula (I) include preferably trans-N-(4-((2S, 6R)-2,6-dimethylmorpholino)phenyl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide, trans-N-(6-(5,6-dihydropyridin-1(2H)-yl)pyridin-3-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, trans-N-(6-(4-trifluoromethyl)phenyl)pyridin-3-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, trans-N-(6-fluorobenzo[d]thiazol-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide, trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide (S-2367), and the following compounds.

[Chemical formula 10]



A particularly preferable compound is

trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide (S-2367). The compound is a crystal under a room temperature.

[0015]

The amount of an NPY₅ receptor antagonist, especially S-2367, in the preparation of the present invention is preferably within a scope in which the drug is efficacious and its solubility can be improved. The scope is (1) usually, 5 to 50% by weight, (2) preferably, 10 to 40% by weight, (3) more preferably, 15 to 30% by weight, (4) further preferably, 20 to 30% by weight, and (5) particularly preferably, 25 to 30% by weight, based on the total amount of the preparation. When the amount is less than the scope, there is a possibility that sufficient drug efficacy is not obtained or the volume of the preparation is enlarged and, when the amount is more than the scope, there is a possibility that the solubility cannot be sufficiently improved.

[0016]

The NPY₅ receptor antagonist in the preparation of present invention is not particularly limited as far as the drug can be orally administered, which is preferably a drug having low solubility in water, so-called poorly water-soluble drug. Herein, the solubility of a drug in water refers to that at 37°C in any of water and a buffer having pH 1 to 8 possible as the environment in a digestive tract, representatively, in water, first fluid and second fluid of Dissolution Test in the Japanese Pharmacopoeia. The low solubility is e.g., 100 μ g/mL or less, 50 μ g/mL or less and 10 μ g/mL or less. In particular, the solubility of a poorly water-soluble drug, S-2367 (the solubility of Dissolution Test in Japanese Pharmacopoeia is about 3.5 μ g/mL) can be improved.

[0017]

The amorphous stabilizer preferably stabilizes the amorphous state

by interacting with a fluctuating stage of a crystal lattice after swinging a crystal structure of a poorly water-soluble drug with an amorphousization inducing agent. However, the amorphous stabilizer includes one capable of bringing a crystal of the compounds into the amorphous state without blending the amorphousization inducing agent. Specifically, preferable examples include carboxymethylethylcellulose (CMEC).

[0018]

CMEC is a mixed ether of carboxymethyl and ethyl of cellulose. CMEC, listed in the Japanese Pharmaceutical Excipients, may be used. Preferably, CMEC may contain 8.9 to 14.9% carboxymethyl group ($-\text{CH}_2\text{COOH}$) and 32.5 to 43.0% ethoxyl group ($-\text{OC}_2\text{H}_5$). Specifically, preferable examples include carboxymethylethylcellulose (Sanyo Chemical Industries, Ltd.).

[0019]

The amount of CMEC in the preparation of the present invention is preferably within a scope in which the solubility of the main drug can be improved. The scope is (1) usually, 50 to 95% by weight, (2) preferably, 60 to 90% by weight, (3) more preferably, 70 to 85% by weight, (4) further preferably, 70 to 80% by weight, and (5) particularly preferably, 70 to 75% by weight, based on the total amount of the preparation. When the amount is less than the scope, since the effect of suppressing the crystal precipitation by CMEC is decreased, there is a possibility that a drug is crystallized during a production process, and an amorphous preparation cannot be obtained. When the amount is more than the scope, there is a possibility that the amount of the main drug decreases relatively and the dose of the preparation increase.

[0020]

One of preferable aspects of the present preparation is such that (1) usually, the NPYY5 receptor antagonist is 5 to 50% by weight and CMEC is 50 to 95% by weight, (2) preferably, the NPYY5 receptor antagonist is 10 to 40% by weight and CMEC is 60 to 90% by weight, (3) more preferably, the NPYY5 receptor antagonist is 15 to 30% by weight and CMEC is 70 to 85% by weight, (4) further preferably, the NPYY5 receptor antagonist is 20 to 30% by weight and CMEC is 70 to 80% by weight, and (5) particularly preferably, the NPYY5 receptor antagonist is 25 to 30% by weight, and CMEC is 70 to 75% by weight, based on the total amount of the preparation.

[0021]

One of preferable aspects of the present preparation is such that (1) usually, S-2367 is 5 to 50% by weight and CMEC is 50 to 95% by weight, (2) preferably, S-2367 is 10 to 40% by weight and CMEC is 60 to 90% by weight, (3) more preferably, S-2367 is 15 to 30% by weight and CMEC is 70 to 85% by weight, (4) further preferably, S-2367 is 20 to 30% by weight and CMEC is 70 to 80% by weight, and (5) particularly preferably, S-2367 is 25 to 30% by weight, and CMEC is 70 to 75% by weight, based on the total amount of the preparation.

[0022]

One of preferable aspects of the present preparation is such that the weight ratio of S-2367 and CMEC is (1) usually, S-2367:CMEC = 1:1 to 1:19, (2) preferably, S-2367:CMEC = 1:1.5 to 1:9, (3) more preferably, S-2367:CMEC = 1:2.33 to 1:5.67, (4) further preferably, S-2367:CMEC = 1:2.33 to 1:4, and (5) particularly preferably, S-2367:CMEC = 1:2.33 to 1:3.

[0023]

The amorphousization inducing agent used in the present invention is a compound which changes the crystal lattice energy of a poorly water-soluble drug towards a low energy direction, and has a function/nature of increasing the fluctuation of a crystal lattice at the same temperature. Specifically, the examples include amino acid or a salt thereof (aspartic acid and sodium salt, magnesium salt thereof and the like, glycine, alanine, glutamic acids, glutamic acid hydrochloride and the like), aspartame, erythorbic acid or a salt thereof, ascorbic acid or a salt thereof (sodium salt), stearic acid ester, aminoethylsulfonic acid, inositol, ethylurea, citric acid or a salt thereof (salt of trisodium, disodium, dihydrogen sodium and the like, calcium salt and the like), glycyrrhizic acid or a salt thereof (sodium salt such as trisodium, disodium and the like, ammonium salt such as diammonium, monoammonium and the like, potassium salt and the like), gluconic acid or a salt thereof (sodium salt, calcium salt, magnesium salt and the like), creatinine, salicylic acid or a salt thereof (sodium salt and the like), tartaric acid or a salt thereof (sodium salt, potassium/sodium salt, hydrogen/potassium salt and the like), succinic acid or a salt thereof (sodium salt such as disodium, monosodium and the like), calcium acetate, saccharine sodium, aluminum hydroxide, sorbic acid or a salt thereof (potassium salt and the like), dehydroacetic acid or a salt thereof (sodium salt etc.), sodium thiomalate, nicotinic acid amide, urea, fumaric acid or a salt thereof (sodium salt and the like), macrogols, maltose, maltol, maleic acid, mannitol, meglumine, sodium desoxycholate and phosphatidylcholine.

[0024]

Examples of the amorphousization inducing agent include preferably amino acid or a salt thereof (aspartic acid and sodium salt, magnesium salt thereof and the like, glycine, alanine, glutamic acids and glutamic acid hydrochloride and the like), ascorbic acid or a salt thereof (sodium salt etc.), stearic acid ester, aminoethylsulfonic acid, ethylurea, citric acid or a salt thereof (salt of trisodium, disodium, dihydrogen sodium and the like, calcium salt), glycyrrhizic acid or a salt thereof (sodium salt such as trisodium, disodium and the like), ammonium salt of diammonium, monoammonium and the like, potassium salt and the like), creatinine, tartaric acid or a salt thereof (sodium salt, sodium/potassium salt, hydrogen/potassium salt and the like), succinic acid or a salt thereof (sodium salt such as disodium, monosodium and the like), saccharine sodium, nicotinic acid amide, urea, fumaric acid or a salt thereof (sodium salt and the like), macrogols, maltose, maltol, mannitol, and meglumine.

[0025]

Examples of the amorphousization inducing agent include more preferably amino acid or a salt thereof (aspartic acid and sodium salt, magnesium salt thereof and the like, glycine, alanine, glutamic acids and glutamic acid hydrochloride and the like), ethylurea, glycyrrhizic acid or a salt thereof (sodium salt such as trisodium, disodium and the like, ammonium salt such as diammonium, monoammonium and the like, potassium salt and the like), tartaric acid or a salt thereof (sodium salt, sodium/potassium salt, hydrogen/potassium salt and the like), succinic acid or a salt thereof (sodium salt such as disodium, monosodium and the like), saccharine sodium, nicotinic acid amide, urea, maltose, maltol, mannitol,

and meglumine. Particularly preferable is urea.

[0026]

The amount of amorphousization inducing agent in the preparation of the present invention is preferably within a scope in which the solubility of drug can be improved. The scope is (1) usually, less than 8% by weight, (2) preferably, 0.1 to 6% by weight, (3) more preferably, 0.5 to 5% by weight, (4) further preferably, 1 to 4.5% by weight and (5) particularly preferably, 2 to 4% by weight, based on a total amount of the preparation. Two or more kinds of amorphousization inducing agents may be used in combination and, when they are combined, the total amount thereof is within the scope.

When the amount is less than the scope, there is a possibility that the solubility of drug cannot be increased, and when the amount is more than the scope, there is a possibility that the solubility is decreased, and a side effect of the amorphousization inducing agent is caused, and since the effect of suppressing precipitation of a crystal of the amorphous stabilizer (particularly, water-soluble polymer) during a production process is decreased, there is a great possibility that a drug is easily crystallized upon removal of a solvent, and it is difficult to produce an amorphous preparation.

[0027]

One of preferable aspects of the present preparation is such that (1) usually, the NPY5 receptor antagonist is 5% or more by weight, CMEC is 50% or more by weight and amorphousization inducing agent is less than 8% by weight, (2) preferably, the NPY5 receptor antagonist is 10 to 40% by weight, CMEC is 54 to 89.9% by weight and amorphousization inducing agent is 0.1 to 6% by weight, (3) more preferably, the NPY5 receptor

antagonist is 10 to 30% by weight, CMEC is 65 to 89.5% by weight and amorphousization inducing agent is 0.5 to 5% by weight, (4) further preferably, the NPY₅ receptor antagonist is 10 to 20% by weight, CMEC is 75.5 to 89% by weight and amorphousization inducing agent is 1 to 4.5% by weight, and (5) particularly preferably, the NPY₅ receptor antagonist is 15 to 20% by weight, CMEC is 76 to 83% by weight and amorphousization inducing agent is 2 to 4% by weight, based on the total amount of the preparation.

[0028]

One of preferable aspects of the present preparation is such that (1) usually, S-2367 is 5% or more by weight, CMEC is 50% or more by weight and urea is less than 8% by weight, (2) preferably, S-2367 is 10 to 40% by weight, CMEC is 54 to 89.9% by weight and urea is 0.1 to 6% by weight, (3) more preferably, S-2367 is 10 to 30% by weight, CMEC is 65 to 89.5% by weight and urea is 0.5 to 5% by weight, (4) further preferably, S-2367 is 10 to 20% by weight, CMEC is 75.5 to 89% by weight and urea is 1 to 4.5% by weight, and (5) particularly preferably, the S-2367 is 15 to 20% by weight, CMEC is 76 to 83% by weight and urea is 2 to 4% by weight, based on the total amount of the preparation.

[0029]

Even when the amorphousization inducing agent is not substantially contained in the present solid preparation, the release profile of main drug (particularly S-2367) is sufficiently improved. However, it may be preferable to contain the amorphousization inducing agent, depending on the amount of main drug. In particular, when the amount of S-2367 is 20%, the

release profile is improved by addition of amorphousization inducing agent.

[0030]

In the process for producing the present preparation, preferably, the NPY₅ receptor antagonist (particularly, S-2367), CMEC and optionally, the amorphousization inducing agent are dissolved in a solvent, the solvent is removed, and the resulting solid is ground into a suitable particle size. The solvent in which these raw materials are dissolved is suitable. A specific solvent is water, alcohol, acetone, halogenated carbon and a mixture thereof. Examples of method of removing the solvent include warming under reduced pressure and spray drying.

[0031]

As spray drying method, a spray dryer is used preferably. Preferable producing condition is one by which is the preparation of the present invention produced in good yield. For example, a solution containing about 1 to 20 % main drug as solid concentration is sprayed in condition of outlet temperature 50 to 110 °C.

[0032]

It was revealed that amounts of the amorphous stabilizer, CMEC, and the amorphousization inducing agent in the present solid preparation influence on the solubility and stability of the NPY₅ receptor antagonist. In addition, the stability of main drug in present solid preparation was assessed by confirming the amorphousized state by powder X-ray analysis.

[0033]

The present preparation is obtained in a powder form, a granule form, a mass form of a solid. Even when the present preparation is obtained in a

mass form, grinding or the like can afford a powder. The powder can be also contained in a granule or a tablet. As a diluent, a binder, a lubricant and the like used in the granule or the tablet, conventionally been used one in pharmaceutics can be used. The examples include diluents such as D-mannitol and the like, disintegrating agents such as carmellose calcium and the like, binders such as hydroxypropylcellulose and the like, lubricants such as magnesium stearate and the like, coating agents such as hydroxypropylmethylcellulose and the like.

[0034]

When the dissolution test of the present solid preparation corresponding to 20 mg main drug (e.g., S-2367) in Second method of the Japanese Pharmacopea (paddle method, 50 rpm, second fluid of dissolution test, 900mL) is performed, the dissolution rate after 60 minutes is (1) usually, 4 % or more at 30 minutes, 7 % or more at 60 minutes, 15 % or more at 180 minutes, (2) preferably, 10 % or more at 30 minutes, 15 % or more at 60 minutes, 30 % or more at 180 minutes, (3) more preferably, 30 % or more at 30 minutes, 40 % or more at 60 minutes, 50 % or more at 180 minutes, (4) further preferably, 30 % or more at 40 minutes, 50 % or more at 60 minutes, 60 % or more at 180 minutes, and (5) particularly preferably, 30 % or more at 50 minutes, 60 % or more at 60 minutes, 70 % or more at 180 minutes.

[0035]

In the solid preparation of present invention, a stable preparation keeps the amorphousized state also after preservation. In particular, even after a week preservation in glass vessel at 60 °C, this solid preparation keeps the amorphousized state of main drug (e.g., S-2367).

[0036]

The solid preparation of present invention can increase the release profile of main drug. Therefore, for example, the amount of main drug in the tablet can be decreased. As a result, the size of tablet is downsized. Specially, the amount of tablet containing S-2367 per tablet was about 840 mg before use of the present solid preparation. On the other hand, the use of the present solid preparation leads to a tablet containing about 450 to 550 mg, preferably about 500 mg of S-2367 per tablet, thereby ease of administration was improved.

Examples

[0037]

The following Examples illustrate the present invention in more detail, but which does not limit the present invention at all.

(Process for producing preparation containing CMEC)

Trans-N-(5-trifluoropyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide (S-2367) was used as the NPY₅ receptor antagonist, urea (Wako Pure Chemical Industries, Ltd.) was used as the amorphousization inducing agent, and carboxymethylethylcellulose (CMEC, Sanyo Chemical Industries, Ltd., Standards Compliant for Japanese Pharmaceutical Excipient) was used. S-2367 was produced based on the method described in WO 01/37826 International Publication Pamphlet.

S-2367 and CMEC, each amount shown in Table 1, was added to acetone to dissolve. Then, in case of adding urea, an amount of urea was added to ethanol to dissolve. These solutions were mixed and spray-dried at

the outlet temperature of 80°C using a spray dryer, B-290/B-295 (Buchi), to prepare a solid preparation of present invention as powder state.

[0038]

(Dissolution test method)

The present solid preparation produced by the aforementioned method was subjected to the dissolution test according to the method defined in the 15th revision, Japanese Pharmacopoeia. The concentration of S-2367 was measured using an automatic sampling system (Autosampler W PAS-615 (Toyama Sangyo Co., Ltd.), and spectrophotometer UV-1700 (Shimadzu Corporation)) or 8453 type (Agilent Co.Ltd.). The dissolution test condition is as follows:

- Test method: Japanese Pharmacopoeia, Second Method (paddle method), rotation rate 50 rpm
- Test solution: dissolution test, second fluid, (900 mL, 37°C)
- Test solution collecting time: 0, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, 150, 180 minutes
- Detection wavelength: 243 nm
- Layer length: 5 mm

[0039] (HPLC condition)

- Measuring wavelength: 242 nm
- Column: Capcell Pak C18 MG, 3 μ m, 3.0 $\times$ 50 mm, Shiseido Co., Ltd.
- Column temperature: 35°C
- Mobile phase: methanol/water mixed solution (27 : 73) for HPLC
- Flow rate: about 0.6 mL/min
- Injection amount: 15 μ L

The amount of S-2367 in the dissolution test solution was calculated by the following equation.

(Equation 1)

$$\text{Amount of S-2367 (\%)} = \text{WS} \times (\text{AT/AS}) \times (1/500) \times 100$$

WS: amount of S-2367 standard (mg)

AS: Peak area of standard solution

AT: Peak area of sample solution

1/500: Dilution factor

[0040] (Powder X-ray diffraction)

The powder X-ray diffraction pattern of present solid preparation was investigated using a powder X-ray diffraction apparatus, RINT 2000 (Rigaku Corporation). The powder X-ray diffraction of preparation was measured just after production and after preservation at 60 °C for a week in the glass vessel.

[0041]

Test example 1 The release profile of preparation containing CMEC

Solid preparations of the present invention, in which urea is not contained and each amount of S-2367 and CMEC is as shown in Table 1, were produced by the aforementioned process. A dissolution test of these preparations was performed by the aforementioned method.

[Table 1]

(weight %)

	Example 1	Example 2	Example 3	Example 4	Reference Example 1
S-2367	15.0	20.0	25.0	30.0	50.0
CMEC	85.0	80.0	75.0	70.0	50.0
Total	100.0	100.0	100.0	100.0	100.0

[0042]

A dissolution concentration of S-2367 was investigated with time and, as a result, as shown in Fig.1, when the amount of S-2367 was 15 to 30 % by weight (Example 1 to 4), their release profiles were almost same. The dissolution concentration of S-2367 after 60 minutes of the test was almost 15 to 16 $\mu\text{g} / \text{mL}$ and thereafter kept almost constant concentration. On the other hand, when the amount of S-2367 was 50% by weight (Reference Example 1), while the dissolution rate was higher than that of S-2367 itself, the release profile was not improved.

[0043]

The result of dissolution rate which was converted from dissolution concentration of S-2367 was shown in Fig.2. When the amount of S-2367 was 15 to 30 % by weight, their dissolution rates were almost same. The dissolution rate was almost 60% or more after 60 minutes, and 70% or more after 180 minutes of the test.

[0044]

Test example 2 The stability of preparation containing CMEC after preservation

To confirm the state of main drug (S-2367) in the preparations of Table 1, the measurement of powder X-ray diffraction was performed. As a result, as shown in Figure 3, the crystal peak of S-2367 was not detected just after preparation and S-2367 was converted into amorphous. To the contrary, as shown in Figure 4, the crystal peak of S-2367 was not observed in the preparation containing 15 to 30 % by weight S-2367 after a week storage at 60°C in the glass vessel and the preparations of S-2367 were stable as

keeping the amorphous state. However, the main peak of S-2367 ($2\theta = 16.9, 17.9, 18.9, 20.1^\circ$) was detected in the preparation containing 50% by weight S-2367 and the preparation could not keep the amorphous state.

[0045]

Test example 3 The release profile of preparation containing CMEC and urea

As shown in Table 2 and 3, preparations containing 15 or 20% by weight S-2367 and 4% by weight urea were produced by the aforementioned process and their release profile were investigated.

[Table 2]

	(weight %)	
	Example 1	Example 5
S-2367	15.0	15.0
CMEC	85.0	81.0
Urea	—	4.0
Total	100.0	100.0

[Table 3]

	(weight %)	
	Example 2	Example 6
S-2367	20.0	20.0
CMEC	80.0	76.0
Urea		4.0
Total	100.0	100.0

[0046]

As shown in Figure 5 and 6, in the preparation containing 15 % by weight S-2367, the addition of urea did not almost influence to the dissolution rate. On the other hand, in the preparation containing 20% by

weight S-2367, the addition of urea increased the dissolution rate.

[0047]

Test example 4 The stability after preservation of preparation containing CMEC and urea

To confirm the state of main drug (S-2367) in the preparations containing urea of Table 2 and 3, the measurement of powder X-ray diffraction was performed. As a result, as shown in Figure 7 and 8, the crystal peak of S-2367 was not detected both just after production and preservation at 60°C in glass vessel for a week and the preparations were stable as keeping the amorphous state.

[Industrial applicability]

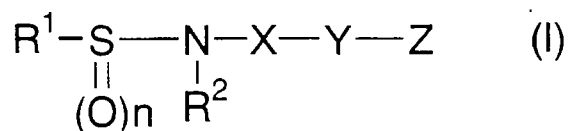
[0048]

The present invention can provide a high stable preparation which improves the solubility in water of the NPY₅ receptor antagonist, especially, trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide.

CLAIMS

1. A solid preparation comprising a compound represented by formula (I):

[Chemical formula 1]



[wherein,

R¹ is optionally substituted lower alkyl, optionally substituted cycloalkyl or optionally substituted aryl,

R² is hydrogen or lower alkyl, and

R¹ and R² taken together may form lower alkylene,

n is 1 or 2,

X is optionally substituted lower alkylene, optionally substituted lower alkenylene, optionally substituted -CO-lower alkylene, optionally substituted -CO-lower alkenylene or

[Chemical formula 2]



[Chemical formula 3]



is optionally substituted cycloalkylene, optionally substituted cycloalkenylene, optionally substituted bicycloalkylene, optionally

substituted arylene or optionally substituted heterocyclediyl and p and q are each independently 0 or 1)

$\cdot\text{NR}^2\cdot\text{X}\cdot$ is

[Chemical formula 4]



(wherein

[Chemical formula 5]



is piperidinediyl, piperazinediyl, pyridinediyl, pyrazinediyl, pyrrolidinediyl or pyrrolediyl, and U is a single bond, lower alkylene or lower alkenylene),

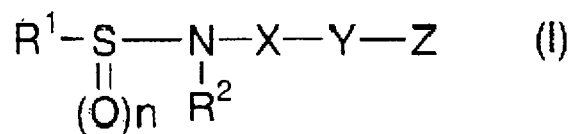
Y is OCONR^7 , CONR^7 , CSNR^7 , NR^7CO or NR^7CS ,

R^7 is hydrogen or lower alkyl,

Z is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted amino, optionally substituted lower alkoxy, optionally substituted carbocyclyl or optionally substituted heterocyclyl] or a prodrug thereof, or a pharmaceutically acceptable salt thereof, or a solvate thereof, and carboxymethylethylcellulose.

2. The solid preparation according to claim 1 comprising a compound represented by formula (I):

[Chemical formula 6]



[wherein X is

[Chemical formula 7]



wherein

[Chemical formula 8]

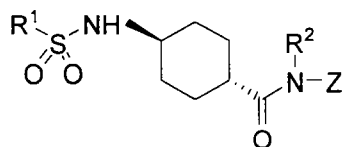


is heterocyclediyl, and R¹ is optionally substituted C₃ to C₁₀ alkyl or optionally substituted C₅ to C₆ cycloalkyl, and the other symbols are the same as defined in claim 1]

or a pharmaceutically acceptable salt thereof, or a solvate thereof, and carboxymethylethylcellulose.

3. The solid preparation according to claim 1 comprising a compound

[Chemical formula 9]



[wherein, R₁ is lower alkyl, R₂ is hydrogen or lower alkyl, Z is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted amino, optionally substituted lower alkoxy, optionally

substituted carbocycle or optionally substituted heterocyclyl]
or a pharmaceutically acceptable salt thereof, or a solvate thereof, and
carboxymethylethylcellulose.

4. The solid preparation according to any one of claims 1 to 3, wherein the content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 5 to 50% by weight.
5. The solid preparation according to claim 4, wherein the content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 15 to 30% by weight.
6. The solid preparation according to claim 4, wherein the content of a compound represented by formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solvate thereof is 25 to 30% by weight.
7. The solid preparation according to any one of claim 1 to 6, wherein a compound represented by formula (I) is trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino)cyclohexanecarboxamide.
8. The solid preparation according to claim 7, which contains 5 to 50% by weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide, and 50 to 95 % by weight of carboxymethylethylcellulose.
9. The solid preparation according to claim 7, which contains 15 to 30% by weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide, and 70 to 85% by weight of carboxymethylethylcellulose.
10. The solid preparation according to claim 7, which contains 25 to 30% by

weight of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide, and 70 to 75% by weight of carboxymethylethylcellulose.

11. The solid preparation according to any one of claims 1 to 10, wherein the content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:1 to 1:19.

12. The solid preparation according to claim 11, wherein the content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:2.33 to 1:5.67.

13. The solid preparation according to claim 11, wherein the content ratio of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiarybutylsulfonylamino) cyclohexanecarboxamide and carboxymethylethylcellulose is 1:2.33 to 1:3.

14. The solid preparation according to any one of claims 1 to 13, which further contains an amorphousization inducing agent.

15. The solid preparation according to claim 14, wherein the amorphousization inducing agent is 1, 2 or more selected from the group consisting of amino acid or a salt thereof, aspartame, erythorbic acid or a salt thereof, ascorbic acid or a salt thereof, stearic acid ester, aminoethylsulfonic acid, inositol, ethylurea, citric acid or a salt thereof, glycyrrhizic acid or a salt thereof, gluconic acid or a salt thereof, creatinine, salicylic acid or a salt thereof, tartaric acid or a salt thereof, succinic acid or a salt thereof, calcium acetate, saccharine sodium, aluminum hydroxide, sorbic acid or a salt thereof, dehydroacetic acid or a salt thereof, sodium thiomalate, nicotinic acid amide, urea, fumaric acid or a salt thereof, macrogols, maltose, maltol,

mannitol, meglumine, sodium desoxycholate and phosphatidylcholine.

16. The solid preparation according to claim 14, wherein the amorphousization inducing agent is urea.

17. The solid preparation according to any one of claims 14 to 16, wherein a content of the amorphousization inducing agent in the preparation is less than 8% by weight.

18. The solid preparation according to claim 17, wherein a content of the amorphousization inducing agent in the preparation is 0.1 to 6 % by weight.

19. The solid preparation according to claim 17, wherein a content of the amorphousization inducing agent in the preparation is 2 to 4 % by weight.

20. The solid preparation according to any one of claims 1 to 13, which does not contain the amorphousization inducing agent.

21. The solid preparation according to any one of claims 1 to 20, which is a solid dispersion.

22. The solid preparation according to any one of claims 1 to 21, which is produced by a spray drying method.

23. A tablet containing the solid preparation according to any one of claims 1 to 22.

24. The tablet according to claim 23, which has a weight of 450 to 550 mg per one tablet.

25. A process for producing the solid preparation according to claim 22, using a spray drying method.

26. A method of improving the solubility of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide, comprising adding carboxymethylethylcellulose to a solid preparation

containing trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide.

27. The method of improving the solubility of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide, comprising adding an amorphousization inducing agent to a solid preparation containing trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide.

28. A method of controlling the release rate of trans-N-(5-trifluoromethylpyridin-2-yl)-4-(tertiary butylsulfonylamino) cyclohexanecarboxamide as 60% or more after 60 minutes and 70% or more after 180 minutes in second fluid of the Japanese Pharmacopoeia, Dissolution Test.