

**4- [2- [[5 -METHYL- 1 - (2 - NAPHTALENYL) -1H - PYRAZOL - 3 - YL] OXY] ETHYL]
MORPHOLINE HYDROCHLORIDE AMORPHOUS SOLID FORMS**

FIELD OF THE INVENTION

The present invention relates to solid forms having a low degree of crystallinity, and to substantially amorphous forms, of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine (P027) and processes for their preparation.

BACKGROUND

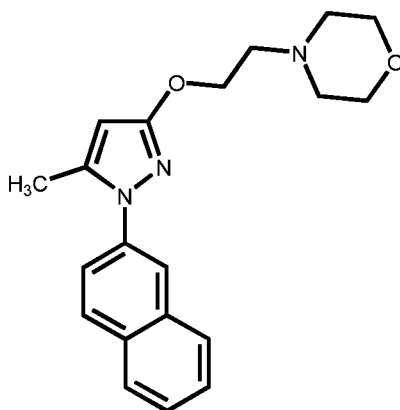
The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of proteins and other biomolecules associated with target diseases. One important class of these proteins is the sigma (σ) receptor, a cell surface receptor of the central nervous system (CNS) which may be related to the dysphoric, hallucinogenic and cardiac stimulant effects of opioids. From studies of the biology and function of sigma receptors, evidence has been presented that sigma receptor ligands may be useful in the treatment of psychosis and movement disorders such as dystonia and tardive dyskinesia, and motor disturbances associated with Huntington's chorea or Tourette's syndrome and in Parkinson's disease (Walker, J.M. et al, *Pharmacological Reviews*, 1990, 42, 355). It has been reported that the known sigma receptor ligand rimcazole clinically shows effects in the treatment of psychosis (Snyder, S.H., Largent, B.L. J. *Neuropsychiatry* 1989, 1, 7). The sigma binding sites have preferential affinity for the dextrorotatory isomers of certain opiate benzomorphans, such as (+)SKF 10047, (+)cyclazocine, and (+)pentazocine and also for some narcoleptics such as haloperidol.

The sigma receptor has at least two subtypes, which may be discriminated by stereoselective isomers of these pharmacoactive drugs. SKF 10047 has nanomolar affinity for the sigma 1 (σ -1) site, and has micromolar affinity for the sigma 2 (σ -2) site. Haloperidol has similar affinities for both subtypes. Endogenous sigma ligands are not known, although progesterone has been suggested to be one of them. Possible sigma-site-mediated drug effects include modulation of glutamate receptor function,

neurotransmitter response, neuroprotection, behavior, and cognition (Quirion, R. et al. *Trends Pharmacol. Sci.*, 1992, 13:85-86). Most studies have implied that sigma binding sites (receptors) are plasmalemmal elements of the signal transduction cascade. Drugs reported to be selective sigma ligands have been evaluated as antipsychotics (Hanner, M. et al. *Proc. Natl. Acad. Sci.*, 1996, 93:8072-8077). The existence of sigma receptors in the CNS, immune and endocrine systems have suggested a likelihood that it may serve as link between the three systems.

In view of the potential therapeutic applications of agonists or antagonists of the sigma receptor, a great effort has been directed to find selective ligands. Thus, the prior art discloses different sigma receptor ligands. 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine is one of such promising sigma receptor ligands. The compound and its synthesis are disclosed and claimed in WO2006/021462.

4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine is a highly selective sigma-1 (σ -1) receptor antagonist. It has displayed strong analgesic activity in the treatment and prevention of chronic and acute pain, and particularly, neuropathic pain. The compound has a molecular weight 337.42 uma. The structural formula of the compound is:



The solid state physical properties of a pharmaceutical compound can be influenced by the conditions under which the compound is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid which affects the ease with which the compound is handled during processing into a pharmaceutical product. Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences because it imposes an upper limit

on the rate at which an orally administered active ingredient can reach the blood. The solid-state form of a compound may also affect its solubility, bioavailability, behavior on compaction, stability, or its electrostatic nature.

Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline or amorphous form in the solid state. In general, polymorphism is caused by the ability of the molecule of a substance to change its conformation or to form different inter molecular and intramolecular interactions, particularly hydrogen bonds, which is reflected in different atom arrangements in the crystal lattices of different polymorphs. Accordingly, polymorphs are distinct solids sharing the same molecular Formula, having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family.

The discovery of new crystalline polymorphic or amorphous forms of a pharmaceutical compound provides an opportunity to improve the physical or performance characteristics of a pharmaceutical product in that it enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics.

The polymorph phase I of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine (P027) and its synthesis are disclosed and claimed in the co-pending application EP 10382025.4 filed on February 4th, 2010. Said polymorph phase I has found to be highly stable over the time with good flow and dissolution characteristics, thus providing advantageous production, handling, storage and therapeutic properties.

Other solid forms of the P027 compound are described in the co-pending application EP10382226.8 filed at the same time as the present one and not published.

Nevertheless, to carry out its pharmaceutical development and release its potential, there is a need in the art for additional solid forms of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine that will facilitate the preparation of better formulations of this active pharmaceutical ingredient. In this regard, alternative morphological forms of the compound may have widely different properties and could either become intermediates for other forms (e.g. the highly stable form I above-mentioned) or provide in themselves a still better formulation of this active

pharmaceutical ingredient. Thus it is important to find such forms, having desirable properties for pharmaceutical use.

BRIEF DESCRIPTION OF THE INVENTION

The inventors of the present invention have surprisingly found and demonstrated that new solid forms of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine (P027) may achieve one or more of the above mentioned objectives. The novel amorphous form of P027 herein disclosed is stable over the time, has good flow and dissolution characteristics and notably may be useful as intermediate for other forms such as the crystalline form I of P027. In addition, they can be obtained through different procedures and conditions.

Thus, the present invention relates to both substantially amorphous forms of P027 and forms of P027 having low degrees of crystallinity as well as several processes for their preparation.

In one embodiment, the present invention is directed to a solid form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine having a degree of crystallinity below about 10%, below about 20% or below about 30%.

In another embodiment, the present invention is directed to a substantially amorphous form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine.

Preferably, said amorphous form of P027 has a FTIR spectrum showing characteristic peaks at about: 3421, 3137, 3054, 2959, 2859, 2540, 2447, 1632, 1600, 1557, 1509, 1487, 1442, 1372, 1305, 1290, 1256, 1236, 1199, 1169, 1130, 1100, 1046, 1013, 982, 933, 917, 861, 819 and 748 cm⁻¹.

The preparation of the solid forms of P027, amorphous or with low crystallinity, represents additional embodiments of the present invention. These solid forms of P027 may be obtained by solvent evaporation using a suitable solvent or mixture of solvents.

The solid forms of P027 may be also obtained in polymer induced crystallizations by:

- solvent evaporation;
- antisolvent addition; or

- crystallization from hot saturated solutions.

Preferably, the solvent used in the above processes is water, acetonitrile, isopropanol, methanol or mixtures comprising water.

Another embodiment of the present invention includes the transformation of a P027 solid form having a low degree of crystallinity, including substantially amorphous forms, into a more stable polymorphic form such as phase I form.

A further embodiment of the present invention includes pharmaceutical compositions comprising the above-mentioned solid forms of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine.

These aspects and preferred embodiments thereof are additionally also defined in the claims.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1: Standard PXRD pattern of the amorphous phase of P027 prepared in example 1.

Fig. 2: ^1H NMR spectrum of the amorphous phase of P027 prepared in example 1.

Fig. 3: DSC and TGA analyses of the amorphous phase of P027 prepared in example 1.

Fig. 4: FTIR analysis of the amorphous phase of P027 prepared in example 1.

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found a novel form, concretely an amorphous form, of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine (P027) which provides advantageous production, handling, storage and therapeutic properties. The novel P027 compound amorphous form is stable over the time and has good flow and dissolution characteristics and can be formulated and administered providing stable compositions and good pharmacological properties. Additionally, the amorphous form of P027 may be used for obtaining other forms, such as crystalline phase I form of P027.

As used herein, the term "about" means a slight variation of the value specified, preferably within 10 percent of the value specified. Nevertheless, the term "about" can mean a higher tolerance of variation depending on for instance the experimental technique used. Said variations of a specified value are understood by the skilled person and are within the context of the present invention. Further, to provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

As used herein, "room temperature" or its abbreviation "rt" is taken to mean 20 to 25 °C.

The P027 amorphous form obtained was characterized by powder X-ray diffraction (PXRD), proton nuclear magnetic resonance (¹H-NMR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Fourier-transformed infrared spectroscopy. The present invention is directed in one aspect to the P027 amorphous form in itself, regardless of the technique used for its characterization. Therefore, the techniques and results provided herein are not intended to limit the present invention, but to serve as characterization of the same. The skilled person will be able, given the guidance and results described herein, to compare and characterize using the available techniques a amorphous phase of the compound 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride (P027).

As mentioned, the present invention encompasses both substantially amorphous forms of P027 and forms of P027 having low degrees of crystallinity. Low degrees of crystallinity include a crystallinity below about 10%, below about 20% or below about 30%. The degree of crystallinity may be calculated according to the method described in WO97/41114 with powder X-ray diffraction (XRD), as follows: A thin layer of the triturated sample is smeared onto a cut silicon single crystal zero background holder which is rotated during the measurement. Cu K α radiation and constant or automatic antiscatter and divergence slits were used to obtain a diffractogram from 1 or 2° 2 θ to at least 35°. The % crystallinity is calculated with the formula:

$$\% \text{ crystallinity} = 100 \cdot C / (A + C)$$

C= the area from the peaks in the diffractogram ("the crystalline area"),

A = the area between the peaks and the background ("the amorphous area").

The expression "substantially amorphous form" refers to a form which does not show peaks at the PXRD pattern i.e. a form having a degree of crystallinity equal to about 0%.

The preparation of solid samples of compound P027 was performed in a set of 40 solvents (table 1). Solvents were selected according to previous experience with the aim to cover a broad range of properties.

Table 1

Solvents used in the formation of P027 solid forms

Name	Code	Name	Code
Dimethylsulfoxide	DMS	Diethoxymethane	DEM
<i>N,N</i> -Dimethylacetamide	DMA	1,2-Dichloroethane	DCE
<i>N,N</i> -Dimethylformamide	DMF	Isopropanol	IPH
Xylene	XIL	Acetonitrile	ACN
Chlorobenzene	CLB	Cyclohexane	CHE
<i>n</i> -Butanol	NBL	Methyl ethyl ketone	MEC
Methyl isobutyl ketone	MIC	Butyl amine	BUA
Isobutyl acetate	AIB	Ethanol	EOH
Pyridine	PYR	Ethyl acetate	AET
Toluene	TOL	1,1,1-Trichloroethane	TCE
3-Pentanone	POA	<i>n</i> -Hexane	HEX
Propyl acetate	APR	Diisopropyl ether	DIE
Nitromethane	NIM	Tetrahydrofuran	THF
Dioxane	DIX	Methanol	MOH

Water	H ₂ O	Chloroform	CLF
2-Butanol	BUL	Methyl acetate	MAC
<i>n</i> -Heptane	HEP	Acetone	ACE
Dimethylcarbonate	CDM	Methyl <i>tert</i> -butyl ether	MTE
Triethylamine	TEA	Dimethoxymethane	DMM
Isopropyl acetate	AIP	Dichloromethane	DCM

In order to plan the crystallization screening, the solubility of P027 was determined at room temperature in the set of solvents of table 1 using the following methodology (table 2): 10 mg of the delivered sample were suspended at room temperature in 0.2 mL of the corresponding solvent and successive additions (initially 0.2 mL and finally 0.5 mL) of solvent until the solid was completely dissolved or up to a maximum of 8 mL were performed. After each solvent addition the suspension was vigorously stirred for 10–15 minutes and visually inspected to determine if the solid was completely dissolved. Solubility ranges are listed in table 2.

Table 2

Solubility of P027 in different solvents at room temperature

Solvent	mg/mL	Solvent	mg/mL
Chloroform	> 50	Dimethylcarbonate ²	1-2
Dimethylsulfoxide	> 50	Tetrahydrofuran	< 1.2
Dimethylformamide	> 50	Methyl acetate	< 1.2
Dichloromethane	> 50	Isobutyl acetate	< 1.2
Methanol	> 50	Propyl acetate	< 1.2
Butyl amine	> 50	Xylene	< 1.2
Water	> 50	Isopropyl acetate	< 1.2
<i>N,N</i> -Dimethylacetamide	25-50	Toluene	< 1.2
Nitromethane	25-50	Ethyl acetate	< 1.2

Pyridine	25-50	1,1,1-Trichloroethane	< 1.2
Ethanol	15-25	Methyl isobutyl ketone	< 1.2
1,2-Dichloroethane	15-25	Methyl tert-butyl ether	< 1.2
Acetonitrile ¹	10-20	Dimethoxymethane	< 1.2
<i>n</i> -Butanol ¹	5-10	Cyclohexane	< 1.2
Acetone	4.0-5.0	Chlorobenzene	< 1.2
Isopropanol ¹	4.0-5.0	<i>n</i> -Heptane	< 1.2
2-Butanol ¹	3-4	<i>n</i> -Hexane	< 1.2
Methyl ethyl ketone ¹	2-4	Diisopropyl ether	< 1.2
3-Pentanone ²	1-2	Triethylamine	< 1.2
Dioxane ²	1-2	Diethoxymethane	< 1.2

¹The solid was dissolved at 60 °C. The solution was left at room temperature and no solid was observed.

²The solid was dissolved at 80 °C. The solution was left at room temperature and no solid was observed.

The solvents in which P027 was insoluble were used as antisolvents (e.g. those solvents providing a solubility < 1.2 mg/mL). For example, *n*-Heptane (HEP) and diisopropyl ether (DIE) were used as antisolvents. The other solvents were used as dissolving solvents in the different crystallization strategies assayed.

In order to cover the broadest crystallization range possible, several crystallization methodologies were employed using the solvents described in table 1. Procedures oriented to obtain the thermodynamically stable phase as well as procedures directed to obtain kinetically favored phases were used. Moreover, solvent mediated as well as solvent free crystallization procedures were assayed. A list of the crystallization procedures used in this invention is following:

- Solvent evaporation at two rates at room temperature
- Solvent evaporation at different temperatures: -21, 4 and 60 °C
- Crystallization from hot saturated solutions at two cooling rates
- Crystallization aimed to the preparation of hydrates

- Crystallization by addition of an antisolvent
- Crystallization by diffusion of an antisolvent
- Grinding experiments
- Pressure experiments
- Slurry experiments

In one embodiment of the present invention, the new P027 solid form, with low crystallinity or substantially amorphous, is obtained by dissolving the P027 compound in a suitable solvent or mixture of solvents and then evaporating the solvent or mixture of solvents to obtain the amorphous form. In a preferred embodiment of the present invention, the solvent is water, a mixture of water and a polar solvent, or a polar solvent. More preferably the solvent is selected from water, acetonitrile, isopropanol, methanol or a mixture comprising water such as a mixture of acetonitrile-water, isopropanol-water or methanol-water. More preferably, the solvent is water or a mixture of acetonitrile-water, isopropanol-water or methanol-water.

According to one variant of this process, the P027 compound may be dissolved at a temperature about room temperature (about 20 to about 25 °C) or above, for instance at a temperature ranging from about room temperature to about 120 °C. In another variant to this process, the P027 amorphous form may be obtained when the solvent is evaporated at a temperature ranging from about 40 °C to about 60 °C. Likewise, the solvent can be conveniently evaporated at about room temperature or above.

Additionally to the standard crystallization procedures, a new methodology was used applying polymers to induce the crystallization of new solids. As described in the literature, the use of polymers could favor the formation of new crystalline phases (M. Lang *et al. J. Am. Chem. Soc.*, **2002**, 124, 14834; C. Price *et al. J. Am. Chem. Soc.*, **2005**, 127, 5512.). Moreover the presence of polymers could support the formation of larger single crystals and stabilize the formation of solvates. A series of polymers (see table 3) were added in catalytic amounts to a solution of P027 and crystallized using the following methodologies:

- Solvent evaporation at room temperature
- Crystallization by antisolvent addition

- Crystallization from hot saturated solutions
- Grinding experiments

Table 3

Polymers used in this invention

Name	Code
Hydroxipropyl methyl cellulose	HPC
Poly(ethylene glycol)	PGY
Polyvinyl pyrrolidone	PVP
Poly(acrylic acid)	PAA
Nylon 6/6	NYL
Polypropylene	PPL
Poly(styrene-co-divinylbenzene)	PSV
Polyvinylchloride	PVC
Poly(tetrafluoroethylene)	PTF
Poly(vinyl acetate)	PVA
Poly(vinyl alcohol)	PVH
Polyacrylamide	PAD
Polysulfone	PLS
Poly(methyl methacrilate)	PMM

As used herein referring to polymers, “catalytic amounts” represent a substoichiometric amount of polymer with respect to the compound P027; preferably below a 25% wt of the amount of compound P027. In a particular embodiment, “catalytic amounts” represent below a 20% wt of the compound P027. In a more particular embodiment, “catalytic amounts” represent below a 10% wt of the compound P027.

In the experiments of crystallization using polymers, the solvent was selected from the above-mentioned list for the experiments without polymers. In a preferred embodiment of the present invention, when using polymers the solvent is water, a mixture of water and a polar solvent, or a polar solvent. More preferably the solvent is selected from water, acetonitrile, isopropanol, methanol or a mixture comprising water such as a mixture of acetonitrile-water, isopropanol-water or methanol-water. More preferably, solvent is water or methanol.

In the experiments of crystallization using polymers by solvent evaporation or by antisolvent addition, the P027 compound may be dissolved at a temperature about room temperature (about 20 to about 25 °C) or above, for instance at a temperature ranging from about room temperature to about 120 °C. Then, the solvent can be conveniently evaporated at about room temperature or above.

In the experiments of crystallization using polymers from hot saturated solutions, the temperature may depend on the solvent used. For example, a temperature about 100 °C is suitable for water.

All solids obtained using the different crystallization methodologies were characterized by PXRD and classified according to the different PXRD patterns obtained. Further analyses performed were also taken into account for the classification of the solids. (see experimental section).

The standard PXRD pattern of the amorphous phase obtained is represented in Figure 1. As expected, no peaks were observed. PXRD was used for evaluating the stability of the amorphous phase as well.

In addition, several samples of the amorphous form obtained were analyzed by ^1H NMR in order to check the stability of the salt (figure 2 is a ^1H NMR spectrum of the amorphous phase). The chemical shifts and the integrations of the ^1H NMR signals were coincident for all samples and no signs of the loss of HCl or decomposition of the samples could be observed.

A DSC analysis of amorphous form samples was performed with a heating rate of 10 °C/min. The DSC analysis presents a broad exothermic peak with an onset at 105 °C and an enthalpy of 83 Jg⁻¹, probably due to the loss of water overlapped with recrystallization of the sample, and a sharp endothermic peak with an onset at 194 °C

and an enthalpy of 95 Jg^{-1} , due to the fusion of phase I followed by decomposition (see Figure 3).

The TGA analysis of an amorphous form sample showed a weight loss of 2.4 % between 40 and 140 °C. Decomposition on melting of the sample was observed at temperatures higher than 190 °C (see Figure 3).

The FTIR spectrum of P027 amorphous presented intense peaks at about: 3421, 3137, 3054, 2959, 2859, 2540, 2447, 1632, 1600, 1557, 1509, 1487, 1442, 1372, 1305, 1290, 1256, 1236, 1199, 1169, 1130, 1100, 1046, 1013, 982, 933, 917, 861, 819 and 748 cm^{-1} (see Figure 4).

Another further embodiment of the present invention includes the transformation of a P027 solid form having a low degree of crystallinity, including substantially amorphous forms, into a more stable polymorphic form such as phase I form.

A further embodiment of the present invention includes pharmaceutical compositions comprising the above-mentioned solid forms of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine.

Having described the invention in general terms, it will be more easily understood by reference to the following examples which are presented as an illustration and are not intended to limit the present invention.

EXAMPLES

Equipment used in the characterization of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride amorphous form.

a) Powder X-ray Diffraction analysis (PXRD)

Approximately 20 mg of the non manipulated samples were prepared in standard sample holders using two foils of polyacetate.

Powder diffraction patterns were acquired on a D8 Advance Series 2Theta/Theta powder diffraction system using $\text{Cu}_{K\alpha}$ -radiation in transmission geometry (Wavelength: $1.54060 \text{ \AA}$). The system was equipped with a VÄNTEC-1 single photon counting PSD, a Germanium monochromator, a ninety positions auto changer sample stage, fixed

divergence slits and radial soller. Programs used: Data collection with DIFFRAC plus XRD Commander V.2.5.1 and evaluation with EVA V.12.0.

b) Proton Nuclear Magnetic Resonance (^1H NMR)

Proton nuclear magnetic resonance analyses were recorded in deuterated chloroform (CDCl_3) in a Bruker Avance 400 Ultrashield NMR spectrometer, equipped with a z-gradient 5 mm BBO (Broadband Observe) probe with ATM and an automatic BACS-120 autosampler. Spectra were acquired solving 2–10 mg of sample in 0.6 mL of deuterated solvent.

c) Differential Scanning Calorimetry analysis (DSC)

Standard DSC analyses were recorded in a Mettler Toledo DSC822e. Samples of 1-2 mg were weighted into 40 μL aluminium crucibles with a pinhole lid, and were heated, under nitrogen (50 mL/min), from 30 to 300 $^{\circ}\text{C}$ at 10 $^{\circ}\text{C}/\text{min}$. Data collection and evaluation was done with software STARe.

d) Thermogravimetric analysis (TGA)

Thermogravimetric analyses were recorded in a Mettler Toledo SDTA851e. Samples of 3-4 mg were weighted (using a microscale MX5, Mettler) into open 40 μL aluminium crucibles with a pinhole lid, and heated at 10 $^{\circ}\text{C}/\text{min}$ between 30 and 500 $^{\circ}\text{C}$, under nitrogen (80 mL/min). Data collection and evaluation was done with software STARe.

e) Fourier Transform Infrared analysis (FTIR)

The FTIR spectra were recorded using a Bruker Tensor 27, equipped with a MKII golden gate single reflection ATR system, a mid-infrared source as the excitation source and a DTGS detector. The spectra were acquired in 32 scans at a resolution of 4 cm^{-1} . No sample preparation was required to perform the analysis.

Example 1

Preparation and characterization of P027 amorphous form

0.2 g of compound P027 was dissolved in 4.8 mL of water at room temperature. The resulting solution was left to evaporate in a Petri plate at 60 °C. The resulting oil solidified and the solid obtained was analyzed by PXRD, ¹H NMR, DSC, TGA, FTIR and KF.

P027 amorphous form was also prepared with solvent mixtures comprising water. The solutions were prepared from 20 mg of compound P027 in 0.2 ml of the solvent/water mixture at 60 °C. The ratio of the solvents used and the crystallization time was respectively:

- Acetonitrile/H₂O 75/25 for 1 month;
- Isopropanol/H₂O 25/75 for 1 month; and
- Methanol/H₂O 50/50 and 25/75 for 1 month.

K.F. analysis: 3.6 ± 0.1 % (theoretical 3.04 %).

The characterisation of P027 amorphous form is the following (Figures 2-4):

¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H), 3.04-3.13 (m, 2H), 3.46-3.50 (m, 2H), 3.56 (d, J = 12 Hz, 2H), 3.97 (dd, J = 13 Hz, J = 3 Hz, 1H), 4.27-4.34 (m, 2H), 4.79-4.82 (m, 2H), 5.73 (s, 1H), 7.49-7.57 (m, 3H), 7.80-7.92 (m, 4H) ppm.

DSC (10 °C/min): The DSC analysis presents a broad exothermic peak with an onset at 105 °C and an enthalpy of 83 Jg⁻¹, probably due to the lost of water overlapped with recrystallization of the sample, and a sharp endothermic peak with an onset at 194 °C and an enthalpy of 95 Jg⁻¹, due to the fusion of phase I followed by decomposition.

TGA (10 °C/min): A weight loss in the range between 40 and 140 °C of 2.4 % and a weight loss starting at around 190 °C corresponding to decomposition on melting.

FTIR (ATR): 3421, 3137, 3054, 2959, 2859, 2540, 2447, 1632, 1600, 1557, 1509, 1487, 1442, 1372, 1305, 1290, 1256, 1236, 1199, 1169, 1130, 1100, 1046, 1013, 982, 933, 917, 861, 819 and 748 cm⁻¹.

The scale-up of the amorphous phase was performed by evaporation of a solution in water of P027 at higher temperatures using 100, 200, 300 and 500 mg of compound. The results obtained in each case are gathered in table 4.

Table 4
Scale-up of the amorphous phase

Entry	Scale ¹	N° exp.	Procedure	Solvent	Observations
1	100 mg	1	Solvent evaporation at 40 °C	water	amorphous
2	100 mg	1	Solvent evaporation at 50 °C	water	amorphous
3	100 mg	1	Solvent evaporation at 60 °C	water	amorphous
4	200 mg	4	Solvent evaporation at 60 °C	water	amorphous
5	300 mg	5	Solvent evaporation at 60 °C	water	amorphous

1)-Referred to starting compound P027.

In the scale up, the experiments performed at 100, 200 and 300 mg scale, gave the amorphous phase.

Example 2

Stability evaluation of the P027 amorphous form obtained

In order to test the stability of the amorphous phase and to investigate its stability, different portions of the amorphous phase were dried for four hours at different temperatures (table 5). Once the samples were dried the solid was analyzed by PXRD. In the drying experiments performed at temperatures up to 60 °C for four hours, amorphous phase was recovered. At temperatures over 60 °C, the amorphous phase transformed slightly to a crystalline phase, not clearly identified. After drying for four hours at temperature higher than 100 °C the amorphous phase transformed clearly to phase I.

Table 5

Results for the drying experiments of the amorphous phase

Code	Temperature (°C)	Solid phase
Sample 1	rt	amorphous
Sample 2	40	amorphous
Sample 3	50	amorphous
Sample 4	60	amorphous
Sample 5	80	amorphous + crystalline
Sample 6	90	amorphous + crystalline
Sample 7	100	phase I + crystalline
Sample 8	110	phase I
Sample 9	120	phase I

In a second experiment, different portions of the amorphous phase were dried under vacuum conditions (5-7 mbar) at room temperature, 40 °C and 60 °C for different times (4, 8, 16 and 24 hours; table 6). Once the samples were dried, the solid was analyzed by PXRD. In the experiments performed under vacuum at room temperature the amorphous phase did not change after drying. In the experiments performed at 40 °C the amorphous phase began to crystallize after 16 hours. In the experiments performed at 60 °C the amorphous phase began to crystallize after 8 hours and phase I could be clearly identified after 16 hours.

Table 6

Results for the drying experiments of the amorphous phase

Code	Time (hours)	Solid phase
23 °C		
Sample 10	4	amorphous
Sample 11	8	amorphous
Sample 12	16	amorphous
Sample 13	24	amorphous
40 °C		
Sample 14	4	amorphous

Sample 15	8	amorphous
Sample 16	16	amorphous + phase I
Sample 17	24	amorphous + phase I
60 °C		
Sample 18	4	amorphous
Sample 19	8	amorphous + phase I
Sample 20	16	phase I
Sample 21	24	phase I

Example 3

Crystallization screening using catalytic amounts of polymers for obtained the amorphous form

Selection of polymers

With the aim to induce the formation of new crystalline forms of P027, catalytic amounts of polymers were added to the crystallization experiments. The polymers used are listed in table 3.

Solvent evaporation at room temperature

Samples of P027 (20-25 mg) were dissolved in the minimum amount of the corresponding solvent at room temperature and a small quantity of polymer (4-5 mg) was added to the corresponding solution (tables 7 and 8). The resulting solutions or suspensions were left to evaporate in open vials at room temperature. All solid samples were analyzed by PXRD.

Table 7

Results from fast evaporation experiments at room temperature with water

Polymer	V (mL)	PXRD pattern
Hydroxipropyl methyl cellulose	0.7	amorphous
Polyvinyl pyrrolidone	0.7	amorphous
Poly(acrylic acid)	0.7	amorphous
Poly(styrene-co-divinylbenzene)	0.7	amorphous
Polyvinylchloride	0.7	amorphous

Polyacrilamide	0.7	amorphous
Polysulfone	0.7	amorphous

Table 8

Results from fast evaporation experiments at room temperature with methanol

Polymer	V (mL)	PXRD pattern
Hydroxipropyl methyl cellulose	0.7	amorphous
Polyacrilamide	0.7	amorphous
Polysulfone	0.7	amorphous

Crystallization by addition of an antisolvent

Diisopropyl ether (DIE) was selected as antisolvent for the crystallization experiments by addition of an antisolvent. Samples of P027 (20-25 mg) with the corresponding polymer (5-6 mg) were dissolved in the minimum amount of the dissolving solvent at room temperature and the antisolvent was added under vigorous stirring (table 9). When solids were obtained after antisolvent addition, they were separated by centrifugation. If not, the solution was left to evaporate at room temperature. The solids obtained were analyzed by PXRD.

Table 9

Results from crystallization experiments in water by addition of an antisolvent

Polymer	Crystallization	PXRD
Poly(acrylic acid)	Evaporation	amorphous
Poly(styrene-co-divinylbenzene)	Evaporation	amorphous
Polyvinylchloride	Evaporation	amorphous
Poly(vinyl alcohol)	Evaporation	amorphous
Polyacrilamide	Evaporation	amorphous

Crystallization from hot saturated solutions

Samples with P027 (20-30 mg) and the corresponding polymer (4-5 mg) were dissolved in the minimum amount of the corresponding solvent at high temperature to obtain a saturated solution and slowly cooled to room temperature (table 10). When solids were obtained after cooling at room temperature, they were separated by centrifugation. If not, the solutions were left evaporating up to dryness at room temperature. All the solids obtained were analyzed by PXRD.

Table 10

Results from crystallization experiments from hot saturated solutions in water at 100°C

Polymer	V (mL)	Crystallization conditions	PXRD pattern
Hydroxipropyl methyl cellulose	0.2	Evaporation	amorphous
Nylon 6/6	0.2	Evaporation	amorphous
Poly(styrene-co-divinylbenzene)	0.2	Evaporation	amorphous
Polyvinylchloride	0.2	Evaporation	amorphous
Poly(tetrafluoroethylene)	0.2	Evaporation	amorphous
Poly(vinyl acetate)	0.2	Evaporation	amorphous
Poly(vinyl alcohol)	0.2	Evaporation	amorphous
Polyacrilamide	0.2	Evaporation	amorphous
Polysulfone	0.2	Evaporation	amorphous
Poly(methyl methacrilate)	0.2	Evaporation	amorphous

CLAIMS

1. A solid form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine having a degree of crystallinity below 30%.
- 5 2. The solid form according to claim 1, which is substantially amorphous.
3. The solid form according to claim 2, having a FTIR spectrum showing characteristic peaks at about: 3421, 3137, 3054, 2959, 2859, 2540, 2447, 1632, 1600, 1557, 1509, 1487, 1442, 1372, 1305, 1290, 1256, 1236, 1199, 1169, 1130, 1100, 1046, 1013, 982, 933, 917, 861, 819 and 748 cm⁻¹.
- 10 4. A process for the preparation of a solid form as defined in any of claims 1 to 3, comprising:
 - a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in a suitable solvent or mixture of solvents, and
 - 15 b) evaporating the solvent or solvents.
5. The process according to claim 4, wherein 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride is dissolved at a temperature ranging from about room temperature to 120 °C.
6. The process according to claim 4, wherein the solvent is evaporated at about
20 room temperature or above.
7. A process for the preparation of a solid form as defined in any of claims 1 to 3, comprising:
 - a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in a suitable solvent or mixture of
25 solvents in the presence of catalytic amounts of a polymer selected from the group: hydroxipropyl methyl cellulose, polyvinyl pyrrolidone, poly(acrylic acid), poly(styrene-co-divinylbenzene), polyvinylchloride, polyacrilamide, polysulfone; and b) evaporating the solvent or solvents;
 - a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-
30 1H-pyrazol-3-yl]oxy]ethyl]morpholine in a suitable solvent or mixture of solvents in the presence of catalytic amounts of a polymer selected from the group: poly(acrylic acid), poly(styrene-co-divinylbenzene),

polyvinylchloride, poly(vinyl alcohol, and polyacrilamide; and b) adding diisopropyl ether as antisolvent; or

- 5 - crystallization from a hot saturated solution of a suitable solvent or mixture of solvents in the presence of catalytic amounts of a polymer selected from the group: hydroxipropyl methyl cellulose, nylon 6/6, poly(styrene-co-divinylbenzene), polyvinylchloride, poly(vinyl acetate), poly(vinyl alcohol), polyacrilamide, polysulfone or poly(methyl methacrilate).

10 **8.** The process according to claims 4 or 7, wherein the suitable solvent or mixture of solvents are selected from the group consisting of water, acetonitrile, isopropanol, methanol, acetonitrile-water, isopropanol-water and methanol-water.

9. Use of a solid form as defined in any of claims 1 to 3 for preparing crystalline form phase I.

15 **10.** A pharmaceutical composition comprising a solid form as defined in any of claims 1 to 3.