BRIEF DESCRIPTION ~~OF THE INVENTION~~

The inventors of the present ~~invention~~ disclosure 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 polymorphic and solvated forms of P027 herein disclosed are fairly stable over the time and have good flow and dissolution characteristics. Particularly, a novel and highly stable crystalline form of the P027 compound (phase I form) provides advantageous production, handling, storage and therapeutic properties. Further, some of the new solid forms of P027 may be useful as intermediates for other useful forms such as the crystalline phase I form of P027.

Thus, the present ~~invention~~ disclosure relates to polymorphic forms and solvates of P027, to their use and to several processes for their preparation.

The hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine (P027) can be prepared by contacting a solution of the base with hydrochloric acid. The P027 compound has a molecular weight 373.88 uma, a pKa of 6.73 and a melting point of 194.2 ºC. The compound is very soluble in water and freely soluble in methanol, 1N hydrochloric acid and dimethyl sulphoxide. It is sparingly soluble in ethanol, slightly soluble in acetone and practically insoluble in ethyl acetate and in 1N sodium hydroxide. The product exhibits a better dissolution and absorption profile in vivo than its related base.

~~In one embodiment, t~~The present ~~invention~~ disclosure is directed to a solid polymorphic or solvated form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine.

Preferably, said solid form is selected from the group consisting of:

- P027 phase I form, which can be characterized because it has a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ] of about 5.9, 8.1, 11.3, 11.7, 14.2, 15.1, 15.8, 16.3, 16.8, 17.8, 18.1, 18.6, 19.8, 20.9, 21.9, 22.8, 23.0, 23.2, 23.6, 23.9, 24.3, 25.0, 25.1, 28.0, 28.3, 28.6, 29.0, 29.2, 30.7, and 30.9, with the 2θ values being obtained using copper radiation ($Cu_{K\alpha1}$ 1.54060Å).

- P027 phase II form, which can be characterized because it has a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ] of about the values indicated below in table 1:

- P027 chloroform solvate, which can be characterized because it has a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ] of about the values indicated below in table 5:

Table 5

List of selected peaks obtained by powder X-Ray diffraction of the chloroform solvate

Angle (2θ)	d value (Å)	Intensity (%)
11,370	7,77642	10,0
13,396	6,60439	0,9
14,048	6,29920	1,1
15,010	5,89751	33,5
15,303	5,78539	4,0
16,117	5,49492	4,2
16,804	5,27165	1,5
17,040	5,19923	6,6
17,830	4,97065	2,1
18,029	4,91633	8,4
18,661	4,75106	11,3
18,859	4,70167	7,1
19,190	4,62136	2,9
20,150	4,40334	3,1
20,434	4,34278	1,1
21,424	4,14416	2,5
22,279	3,98707	100,0
22,871	3,88527	16,8
23,449	3,79074	9,1
23,918	3,71738	0,9
24,343	3,65347	3,1
24,709	3,60019	4,6
24,820	3,58439	1,8
25,459	3,49576	16,4
26,199	3,39873	7,6

According to another embodiment, the crystalline P027 phase I form of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride according to the present ~~invention~~ disclosure has a monoclinic unit cell with the following approximate dimensions:

a = 29.4(3) Å

b = 11.7(11) Å

c = 11.0(10) Å

α = 90°

β = 91.3 (2)

γ = 90°

The preparation of the above polymorphic and solvated forms represents additional embodiments of the present ~~invention~~disclosure.

The P027 phase I form can be prepared by crystallizing the P027 compound in various solvents by means of various techniques such as: solvent evaporation at varying temperatures, crystallization from hot saturated solutions, crystallization by antisolvent addition, crystallization by antisolvent diffusion, crystallization from water and solvents mixtures and the preparation of suspensions.

P027 phase II form may be obtained in polymer induced crystallizations by solvent evaporation.

P027 phase III form may be obtained in polymer induced crystallizations either by solvent evaporation or by crystallization by antisolvent addition.

P027 phase IV form may be obtained in polymer induced crystallizations by crystallization by antisolvent addition.

P027 dioxane solvate may be obtained by solvent drop grinding in dioxane or by crystallization from a hot saturated solution of dioxane.

P027 chloroform solvate may be obtained in polymer induced crystallizations either by solvent (chloroform) evaporation or by crystallization from hot saturated solutions of chloroform.

Another embodiment of the present ~~invention~~ disclosure includes the transformation of crystalline forms phase II, phase III and phase IV above into a more stable polymorphic form such as P027 phase I form.

Another embodiment of the present ~~invention~~ disclosure includes the transformation of a solvate of P027, preferably chloroform solvate, into a more stable polymorphic form such as phase I form.

A further embodiment of the present ~~invention~~ disclosure includes pharmaceutical compositions comprising at least one of the forms of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine above-mentioned, particularly P027 phase I, P027 phase II, P027 phase III, P027 phase IV, P027 chloroform solvate and P027 dioxane solvate.

In an aspect, there is provided a solid form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine, which is the polymorphic phase I form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.9, 8.1, 11.3, 11.7, 14.2, 15.1, 15.8, 16.3, 16.8, 17.8, 18.1, 18.6, 19.8, 20.9, 21.9, 22.8, 23.0, 23.2, 23.6, 23.9, 24.3, 25.0, 25.1, 28.0, 28.3, 28.6, 29.0, 29.2, 30.7, and 30.9;

with the 2θ values being obtained using copper radiation ($Cu_{K\alpha1}$ 1.54060 Å).

In another aspect, there is provided a polymorphic or solvated solid form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine, which is selected from the group consisting of:

a) a polymorphic phase II form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.776, 11.629, 14.558, 15.737, 15.891, 16.420,16.740, 17.441, 17.635, 18.056, 18.219, 19.232, 19.712, 20.140, 20.685, 21.135, 21.889, 22.108, 22.478, 22.763, 23.219, 23.454, 23.782, 24.689, 25.065, and 25.671;

b) a polymorphic phase III form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.437, 5.714, 10.918, 11.546, 12.704, 13.344, 13.984, 14.505, 15.606, 15.824, 16.164, 16.646, 17.333, 17.837, 18.719, 18.878, 19.236, 19.533, 20.142, 20.689, 21.337, 22.008, 22.929, 23.596, 24.748, 25.064, 25.207, 25.737, and 26.148;

c) a polymorphic phase IV form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.805, 11.685, 15.559, 15.804, 16.397, 16.879, 17.357, 17.465, 17.621, 19.112, 19.435, 19.923, 21.224, 21.987, 22.167, 22.412, 2.852, 23.059, 23.359, 23.855, 24.092, 25.722, 26.054, 26.649, and 27.780;

~~a)~~d) a dioxane solvate having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 4.734, 9.317, 11.390, 13.614, 14.290, 14.815, 16.211, 16.432,16.782, 17.741, 18.056, 18.329, 18.724, 19.070, 19.494, 20.436, 20.762, 21.587, 22.000, 22.935, 23.084, 23.551, 23.891, 24.721, and 25.078; and

e) a chloroform solvate having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 11.370, 13.396, 14.048, 15.010, 15.303, 16.117, 16.804, 17.040, 17.830, 18.029, 18.661, 18.859, 19.190, 20.150, 20.434, 21.424, 22.279, 22.871, 23.449, 23.918, 24.343, 24.709, 24.820, 25.459, and 26.199;

with the 2θ values being obtained using copper radiation ($Cu_{K\alpha1}$ 1.54060 Å).

In another aspect, there is provided a process for the preparation of the polymorphic phase I form as defined above, comprising:

a) dissolving 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride in a suitable solvent, and

b) evaporating the solvent.

In another aspect, there is provided a process for the preparation of the polymorphic phase I form as defined above, wherein a solution comprising 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride and a suitable antisolvent are mixed.

In another aspect, there is provided a process for the preparation of the polymorphic phase I form as defined above, wherein a suspension comprising 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride is prepared.

In another aspect, there is provided a process for the preparation of the polymorphic phase II form as defined above, comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in water in the presence of catalytic amounts of poly(vinyl alcohol), and

b) evaporating the water.

In another aspect, there is provided a process for the preparation of the polymorphic phase III form as defined above, comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in water or acetone in the presence of catalytic amounts of poly(ethylene glycol), and

b) evaporating the water or the acetone;

or comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in water in the presence of catalytic amounts of poly(ethylene glycol), and

b) adding diisopropyl ether as antisolvent.

In another aspect, there is provided a process for the preparation of the polymorphic phase IV form as defined above, comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in chloroform in the presence of catalytic amounts of a polymer selected from the group consisting of: polyvinyl pyrrolidone, poly(acrylic acid), polypropylene, poly(styrene-co-divinylbenzene), poly(tetrafluoroethylene), poly(vinyl alcohol), polyacrylamide and poly(methyl methacrilate), and

b) adding diisopropyl ether as antisolvent.

In another aspect, there is provided a process for the preparation of the dioxane solvate as defined above, comprising a process selected from:

f) solvent drop grinding comprising:

a) charging the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine together with catalytic quantities of dioxane to a ball mill container; and

b) grinding; and

g) crystallization from a hot saturated solution of dioxane.

In another aspect, there is provided a process for the preparation of the chloroform solvate as defined above, comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in chloroform in the presence of catalytic amounts of a polymer selected from the group consisting of poly(ethylene glycol), polyvinyl pyrrolidone, poly(acrylic acid), nylon 6/6, polypropylene, poly(tetrafluoroethylene), poly(vinyl acetate), poly(vinyl alcohol), polyacrylamide and polysulfone; and

b) either evaporating the chloroform or crystallizing in a hot saturated solution of chloroform.

In another aspect, there is provided the use of polymorphic phase II form, polymorphic phase III form, polymorphic phase IV form, dioxane solvate or chloroform solvate as defined above for obtaining the phase I form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine as defined above.

In another aspect, there is provided a process for the preparation of phase I form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine as defined in above comprising the step of heating crystalline forms phase II, phase III and/or phase IV of this compound as defined above at a temperature between 140 °C and 170 °C.

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

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1: Standard PXRD pattern of phase I.

Fig. 2: ^{1}H NMR spectrum of a P027 compound solution.

Fig. 3: DSC and TGA analyses of phase I.

Fig. 4: FTIR analysis of phase I.

Fig. 5: Randomly selected PXRD patterns of different solids corresponding to phase I in which texture effects can be observed.

Fig. 6: PXRD pattern of phase I samples before and after grinding. The standard PXRD pattern of phase I is shown for comparison purposes.

Fig. 7: ^{1}H-NMR spectra of the samples depicted in Figure 6.

Fig. 8: DSC analysis of phase I at a heating rate of 5 °C/min.

Fig. 9: DSC analysis of phase I at a heating rate of 20 °C/min.

Fig. 10: Ortep-Plot (50 %) showing the organic cation and the two independent half chlorine anions contained in the unit cell.

Fig. 11: Ortep-Plot (50 %) showing the structure of phase I. The hydrogen bonds are marked with discontinuous lines.

Fig. 12: Simulated powder diffraction pattern generated from the single crystal data of phase I.

Fig. 13: Comparison of the simulated powder diffraction pattern obtained from single crystal data and the experimentally measured powder diffraction pattern of phase I.

Fig. 14: PXRD pattern of a phase I form obtained by the evaporation *n*-butanol at -21 °C.

Fig. 15: PXRD pattern of a phase I form obtained by the slow crystallization of hot saturated P027 compound solution in methyl ethyl ketone.

Fig. 16: PXRD pattern of a phase I form obtained by crystallization through the addition of a P027 solution in methanol to an *n*-heptane solution.

CLAIMS

1. A solid ~~polymorphic or solvated~~ form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine, which is the polymorphic phase I form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.9, 8.1, 11.3, 11.7, 14.2, 15.1, 15.8, 16.3, 16.8, 17.8, 18.1, 18.6, 19.8, 20.9, 21.9, 22.8, 23.0, 23.2, 23.6, 23.9, 24.3, 25.0, 25.1, 28.0, 28.3, 28.6, 29.0, 29.2, 30.7, and 30.9;
with the 2θ values being obtained using copper radiation ($Cu_{Kα1}$ 1.54060 Å).

2. A polymorphic or solvated solid form ~~according to claim 1~~ of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine, which is selected from the group consisting of:

~~a) a polymorphic phase I form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.9, 8.1, 11.3, 11.7, 14.2, 15.1, 15.8, 16.3, 16.8, 17.8, 18.1, 18.6, 19.8, 20.9, 21.9, 22.8, 23.0, 23.2, 23.6, 23.9, 24.3, 25.0, 25.1, 28.0, 28.3, 28.6, 29.0, 29.2, 30.7, and 30.9;~~

~~b)~~a) a polymorphic phase II form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.776, 11.629, 14.558, 15.737, 15.891, 16.420,16.740, 17.441, 17.635, 18.056, 18.219, 19.232, 19.712, 20.140, 20.685, 21.135, 21.889, 22.108, 22.478, 22.763, 23.219, 23.454, 23.782, 24.689, 25.065, and 25.671;

~~c)~~b) a polymorphic phase III form having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.437, 5.714, 10.918, 11.546, 12.704, 13.344, 13.984, 14.505, 15.606, 15.824, 16.164, 16.646, 17.333, 17.837, 18.719, 18.878, 19.236, 19.533, 20.142, 20.689, 21.337, 22.008, 22.929, 23.596, 24.748, 25.064, 25.207, 25.737, and 26.148;

~~d)~~c) a polymorphic phase IV form~~, preferably~~ having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 5.805, 11.685, 15.559, 15.804, 16.397, 16.879, 17.357, 17.465, 17.621, 19.112, 19.435, 19.923, 21.224, 21.987, 22.167, 22.412, 2.852, 23.059, 23.359, 23.855, 24.092, 25.722, 26.054, 26.649, and 27.780;

~~e)~~d) a dioxane solvate having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 4.734, 9.317, 11.390, 13.614, 14.290, 14.815, 16.211, 16.432,16.782, 17.741, 18.056, 18.329, 18.724, 19.070, 19.494, 20.436, 20.762, 21.587, 22.000, 22.935, 23.084, 23.551, 23.891, 24.721, and 25.078; and

~~f)~~e) a chloroform solvate having a X-ray powder diffraction pattern showing characteristic peaks at a reflection angle [2θ in degrees] of about 11.370, 13.396, 14.048, 15.010, 15.303, 16.117, 16.804, 17.040,

17.830, 18.029, 18.661, 18.859, 19.190, 20.150, 20.434, 21.424, 22.279, 22.871, 23.449, 23.918, 24.343, 24.709, 24.820, 25.459, and 26.199;

with the 2θ values being obtained using copper radiation ($Cu_{K\alpha1}$ 1.54060 Å).

3. A process for the preparation of the polymorphic phase I form as defined in claim ~~2~~1, comprising:

a) dissolving 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride in a suitable solvent, and

b) evaporating the solvent.

4. The process according to claim 3, wherein 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride is dissolved at a temperature ranging from room temperature to 120 °C and/or the solvent is evaporated at a temperature ranging from -21 °C to 60 °C.

5. A process for the preparation of the polymorphic phase I form as defined in claim ~~2~~1, wherein a solution comprising 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride and a suitable antisolvent are mixed.

6. The process according to claim 5, wherein the mixture is performed at a temperature ranging from room temperature to 90 °C.

7. The process according to claim 5, wherein the mixture is performed by a liquid-liquid diffusion or a gas-liquid diffusion.

8. The process according to claim 3, wherein water is added to the solution.

9. A process for the preparation of the polymorphic phase I form as defined in claim ~~2~~1, wherein a suspension comprising 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine hydrochloride is prepared.

10. The process according to claim 9, wherein the suspension is maintained at a temperature ranging from room temperature to 80 °C.

11. A process for the preparation of the polymorphic phase II form as defined in claim 2, comprising:

a) dissolving the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine in water in the presence of catalytic amounts of poly(vinyl alcohol), and

b) evaporating the water.

12. A process for the preparation of the polymorphic phase III form as defined in claim 2, comprising:

b) either evaporating the chloroform or crystallizing in a hot saturated solution of chloroform.

16. Use of polymorphic phase II form, polymorphic phase III form, polymorphic phase IV form, dioxane solvate or chloroform solvate as defined in claim 2 for obtaining the phase I form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine as defined in claim 1.

17. A process for the preparation of phase I form of the hydrochloride salt of 4-[2-[[5-methyl-1-(2-naphthalenyl)-1H-pyrazol-3-yl]oxy]ethyl]morpholine as defined in claim 1 comprising the step of heating crystalline forms phase II, phase III and/or phase IV of this compound as defined in claim 2 at a temperature between 140 °C and 170 °C.

~~**18.** A pharmaceutical composition comprising a solid form as defined in any one of claims 1 to 2.~~