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54	TITLE OF INVENTION

Amorphous form of cell cycle inhibitor

57	ABSTRACT (NOT MORE THAN 150 WORDS)

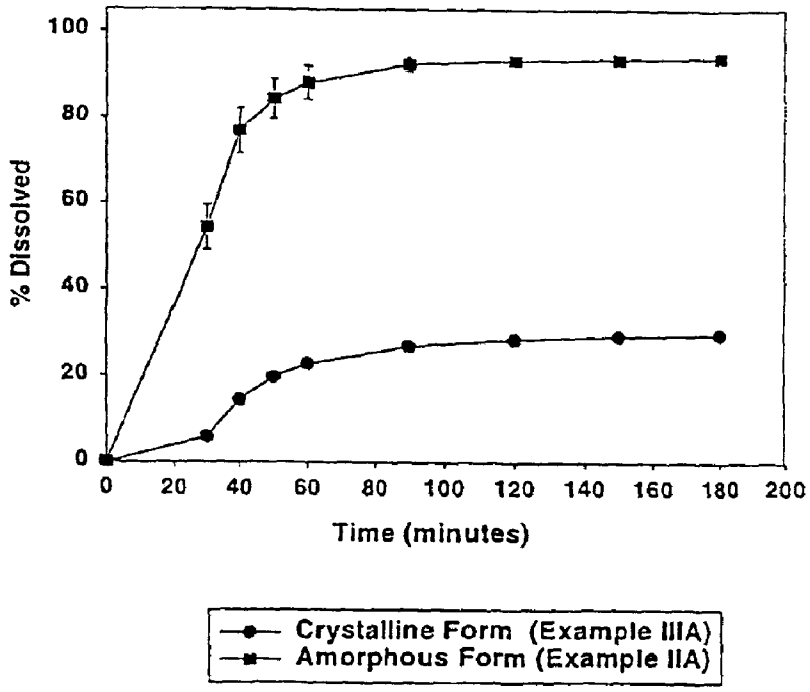
NUMBER OF SHEETS 42

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

A&A P208

Dissolution Profiles of Amorphous Compound of Formula I (Produced in Accordance with Example II A) and of Crystalline Compound (Produced in Accordance with Example III A)

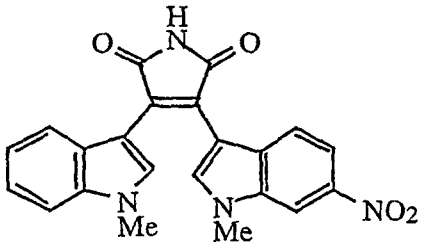


(57) **Abstract:** The present invention provides an amorphous, pharmaceutically active form of a compound of formula (I) which is substantially free of crystalline compound.

Case 20798

Amorphous form of cell cycle inhibitor

The present invention provides an amorphous, pharmaceutically active form of a compound of formula I



I,

which is substantially free of crystalline compound. This compound is also known as 3-(1-methyl-3-indolyl)-4-(1-methyl-6-nitro-3-indolyl)-1H-pyrrole-2,5,-dione. This invention also provides a process for making the, amorphous form of the compound of formula I as well as pharmaceutical compositions including such compound.

A crystalline form of the compound of formula I is known. *See, e.g.,* US Patent No. Re. 36,736. This crystalline form has a melting point of approximately 285 °C (*Id.* column 22, lines 5-6). This compound belongs to a novel class of cell cycle inhibitors and apoptosis-inducers having potent anti-cancer therapeutic activity, in particular in solid tumors such as non-small cell lung, breast and colorectal cancers. *See, e.g.* US Patent No. 6,048,887 and EP 0 988,863. In its previously known crystalline form, compound of formula I has relatively low aqueous solubility (<10 μg/mL) at physiological pHs (which range from 1.5-8.0) and consequently less than optimal bioavailability (less than 5% in

dogs). As this is a therapeutically active compound, it is thus desirable to obtain a form of the compound of formula I which has improved solubility/dissolution rate and bioavailability.

The bioavailability of a therapeutically active compound is generally determined by (i) the solubility/dissolution rate of the compound, and (ii) the partition coefficient/permeability of the compound through a subject's gastrointestinal membrane. The major cause of poor bioavailability of a therapeutically active compound is usually the poor solubility/dissolution rate of said compound. Poor bioavailability is also often accompanied by high variable patient blood levels and unpredictable dose/therapeutic effects due to erratic absorption of the drug by the patient.

Several techniques can be used to improve the bioavailability of therapeutically active compounds having relatively low aqueous solubility. These techniques are discussed in the background Section of EP 0988,863. Also described in EP 0988,863, is a novel process pursuant to which crystalline therapeutically active compounds having relatively low aqueous solubilities may be rendered more bioavailable by being incorporated or dispersed in an ionic polymer.

While the dispersion or incorporation of therapeutically active compounds having relatively low aqueous solubilities in ionic polymers using certain methods may increase the bioavailability of these compounds, these methods can be cumbersome and time consuming. Such methods also require that the therapeutically active compounds are delivered to a patient in combination with a polymer, which may not always be beneficial or desirable. It is thus desirable to develop a process of making the compound of formula I in its amorphous form which does not require dispersion of the compound in a polymer.

The invention relates to an amorphous form of the compound of formula I which is substantially free of the crystalline form of the compound. This amorphous (also referred to as "high energy") form of the compound of formula I exhibits a faster dissolution rate than and superior bioavailability to the previously known crystalline form of the compound. The bioavailability of the amorphous form of the compound of this invention is significantly higher than the crystalline form of the compound, thereby enabling the amorphous form of the compound to be used in the treatment or therapy of cancerous tumors.

Another aspect of the invention relates to stable, amorphous compound of formula I which remains in stable, amorphous form for a period of time to permit the compound to have a reasonable shelf life (for example, two (2) years at room temperature) independent of form stabilizers such as an ionic polymer.

Another aspect of the invention is a process for making the high energy amorphous compound of formula I.

Another aspect of the invention is a pharmaceutical composition including a therapeutically effective amount of the compound of formula I in amorphous form.

Figure 1 is a powder x-ray diffraction pattern of compound of formula I prepared according to previously known methods showing the distinct crystallinity of the compound.

Figure 2 is a powder x-ray diffraction pattern of compound of formula I prepared in accordance with this invention showing the amorphous characteristics of the compound.

Figure 3 is a differential scanning calorimetry thermogram of compound of formula I prepared according to previously known methods_showing a distinct endotherm for the compound thus evidencing that the compound is in crystalline form.

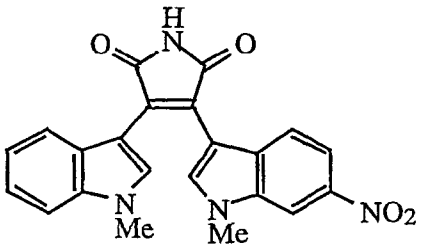
Figure 4 is a differential scanning calorimetry thermogram of the compound of formula I prepared in accordance with this invention showing a glass transition temperature of approximately 112°C thus evidencing that the compound is in amorphous form.

Figure 5 is a powder x-ray diffraction pattern of compound of formula I prepared in accordance with this invention showing that the compound remained in its amorphous form independent of form stabilizers even when exposed to accelerated storage conditions (40°C/75%RH, closed glass vial for 6 months).

Figure 6 is the dissolution profile of preparations containing compound of formula I produced in accordance with previously known methods (Example III A) and

produced in accordance with this invention (Example II A). This figure shows that the compound of the present invention (amorphous form) is much more soluble than the crystalline form of the compound that was previously available.

The present invention provides a high energy, amorphous, pharmaceutically active form of a compound of formula I



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As prepared in accordance with the present invention, the amorphous form of the compound of formula I has very high bioavailability (approximately 15-fold higher) as compared to the crystalline form, enabling the compound to be used in a pharmaceutical product. Not only does the amorphous form of the compound exhibit a superior dissolution rate and bioavailability in contrast to the crystalline form, but due to its high glass transition temperature of approximately 112°C, it retains its amorphous properties independent of form stabilizers.

The amorphous form of compound I according to the present invention significantly facilitates the delivery to a patient of a pharmaceutically active compound that in its crystalline form has relatively low aqueous solubility and poor bioavailability.

As used herein, the following terms shall have the following meanings.

"Amorphous Compound" means that the compound does not exhibit a typical endotherm in a differential scanning calorimetry thermogram and does not have distinct peaks in a powder x-ray diffraction pattern. This form of a compound is also referred to as the "high energy" form of the compound.

"Dissolution Rate" means the speed with which a particular compound dissolves in a particular dissolution medium.

"Form Stabilizers" are substances such as ionic polymers which can be used to immobilize a compound in a particular physical form (e.g. amorphous form) thereby protecting the compound from environmental factors (such as for example heat, moisture, etc.).

"Patient" refers to a human subject.

"Relatively Low Aqueous Solubility" means that a particular compound or form thereof has an aqueous solubility of less than about 10 μg/mL.

"Substantially free of crystalline compound" means that the compound is not more than about 20% crystalline form, preferably not more than about 10% crystalline form.

Methods of Preparation of Amorphous Compound of Formula I

The high energy or amorphous form of the compound of formula I may be prepared by the following methods:

a) Spray Drying or Lyophilization: The compound of formula I,

in a crystalline form, is dissolved in an organic solvent.. Suitable organic solvents for this process include ethanol, methanol, acetone, dimethyl sulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone, diethylene glycol, ethyl ether, glycofural, propylene carbonate, tetrahydrofuran, polyethylene glycols, and propylene glycols. The solvent is then removed by spray drying or lyophilization, yielding amorphous compound of formula I.

b) Solvent Controlled Precipitation: In a preferred embodiment of the invention, crystalline compound of formula I is dissolved in an organic solvent. Suitable organic solvents for this process include those listed above in a). The compound is then precipitated, preferably in aqueous solution, and preferably at a pH where the compound is not soluble. The resulting precipitate is amorphous compound of formula I and can be

recovered by procedures known to those skilled in the art, such as for example, by filtration, centrifugation and washing, etc. The recovered precipitate is then dried (in air, an oven, or a vacuum) and the resulting solid can be further processed, such as milling, pulverizing or micronizing to a fine powder by means known in the art.

c) Supercritical Fluid: Crystalline compound of formula I is dissolved in a supercritical fluid such as liquid nitrogen or liquid carbon dioxide (at supercritical temperature and pressure). The supercritical fluid is then removed by evaporation, leaving the precipitated compound in amorphous form. Alternatively, the compound of formula I is dissolved in an organic solvent as described above in a). A supercritical fluid is used as an anti-solvent for extraction of the organic solvent, causing the compound to precipitate in amorphous form from the organic solvent.

d) Hot Melt Extrusion: Crystalline compound of formula I is fed continuously to a temperature-controlled extruder which is set at different temperature gradients. Specifically, the crystalline compound is extruded and melted in a hot melt extruder, followed by abruptly cooling to room temperature, which causes the compound to solidify or precipitate in amorphous form. The resulting extrudate can then be milled into a fine powder.

The amorphous form of the compound of formula I prepared according to the present invention can then be combined with appropriate pharmaceutically acceptable excipients to yield a pharmaceutical preparation for administration to patients. These excipients include, but are not limited to, inorganic or organic carriers, fillers, binders, disintegrants, lubricants, preservatives, solubilizing agents, stabilizers, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents, antioxidants, and control release agents, all of which are known in the art.

The resulting products from the above-described methods a) - d) can be further processed by means known in the art for incorporation in a pharmaceutical formulation.

This invention also contemplates pharmaceutical preparations that include a therapeutically effective amount of a compound of formula I in amorphous form. A therapeutically effective amount means an amount, at such dosages and for such periods of time, necessary to achieve the desired therapeutic result. Moreover, such amount must be one in which the overall therapeutically beneficial effects outweigh any toxic or undesirable

side effects. A therapeutically effective amount of a compound often varies according to disease state, age and weight of the subject being treated. Thus, dosage regimens are typically adjusted to the individual requirements in each particular case and are within the skill in the art.

The appropriate daily dose of compound I in amorphous form for oral administration to an adult human weighing about 70 kg is from about 100 mg to about 1,500 mg, preferably from about 400 mg to about 800 mg, although the upper limit may be exceeded when indicated. The daily oral dosage can be administered as a single dose or in divided doses, or for parenteral administration, can be given as a continuous infusion.

This invention also contemplates a process for preparing amorphous compound of formula I without dispersing the compound in an ionic polymer.

The invention contemplates a process for the preparation of compound of formula I wherein (a) the crystalline compound of formula I is dissolved in an organic solvent and (b) the desired amorphous compound of formula I is precipitated from the solution of step (a).

Preferably, the organic solvent used in the above process is selected from the group consisting of ethanol, methanol, acetone, dimethyl sulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone, diethylene glycol ethyl ether, glycofural, propylene carbonate, tetrahydrofuran, polyethylene glycols, and propylene glycols. More preferably, the solvent is dimethylacetamide.

Preferably, the precipitation is effected by adding the solution of step (a) to a cold aqueous solution.

Preferably in the above process of the present invention the temperature of the aqueous solution is from about 2°C to about 10 °C and its pH is one in which the compound of formula I in amorphous form is not soluble. Preferably the pH of the aqueous solution is from about 2 to about 7.

The present invention contemplates also for another process for the preparation of compound of formula I, wherein a compound of formula I in crystalline form is dissolved in an organic solvent; and the organic solvent is removed. the organic solvent may be removed by spray drying or by lyophilization.

Preferably the organic solvent is selected from the group consisting of ethanol, methanol, acetone, dimethyl sulfoxide, N, N-dimethylacetamide, N, N-dimethylformamide, N-methylpyrrolidone, diethylene glycol ethyl ether, glycofural, propylene carbonate, tetrahydrofuran, polyethylene glycols, and propylene glycols. More preferably, the organic solvent is removed

The present invention relates also a process for the preparation of compound of formula I wherein a crystalline compound of formula I is dissolved in a supercritical fluid; and the supercritical fluid is removed.

Preferably, the supercritical fluid is liquid nitrogen or liquid carbon dioxide.

The present invention concerns also a process for the preparation of compound of formula I wherein the crystalline compound of formula I is dissolved in an organic solvent; and the organic solvent from the solution is extracted with a supercritical fluid like liquid nitrogen or liquid carbon dioxide

The present invention concerns also a process for the preparation of compound of formula I wherein a crystalline compound of formula I is continuously exposed to a temperature-controlled extruder (hot melt extruder) that is set at different temperature gradients and the extrudate is rapidly cooled.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically carrier for treating tumors. Preferably this pharmaceutical composition is free of form stabilizers.

Preferably this pharmaceutical composition is free of ionic polymers.

The present invention provides also a method for the treatment of tumors in which a compound of formula (I) is administered to a human or an animal.

Finally, the present invention provides the use of compound of formula I for the manufacture of medicament for the treatment of tumors.

The following examples illustrate methods for making the amorphous compound of the present invention as well as pharmaceutical preparations incorporating said

amorphous compound. These examples illustrate the present invention and are not intended to be limiting.

Examples

Example I: General Preparation of Amorphous Compound

Crystalline compound of formula I was dissolved in dimethylacetamide. The resulting solution was then slowly added to cold (2°-10°C) aqueous solution at pH 2-7. This caused the compound to precipitate as amorphous compound. The precipitate was washed several times with cold (2°-10°C) water until the residual dimethylacetamide was below 0.3%. The precipitate was dried and milled into the desirable particle size.

Example II: Preparation of Pharmaceutical Preparations Including Amorphous Compound of formula I

The powder form of the amorphous compound prepared in accordance with Example I above was then incorporated with various pharmaceutical excipients to yield the following pharmaceutical formulations:

Example IIA

Formulation	% w/w
Amorphous Compound of Formula I	50
Lactose Anhydrous	50

Method of Preparation of Formulation:

1. Amorphous compound of formula I (with a mean particle size of 8 microns as determined by a laser light scattering instrument), which was prepared in accordance with Example I, was mixed with lactose anhydrous in a mixer for 10 minutes.

2. The resulting powder blend form Step 1 was encapsulated into a capsule.

Example IIB

Formulation	% w/w
Amorphous Compound of Formula I	50
Methocel K100LV	40
Microcrystalline Cellulose	7
Talc	2
Magnesium Stearate	1

Method of Preparation of Formulation:

1. Amorphous compound of formula I (with a mean particle size of 8 microns as determined by a laser light scattering instrument), which was prepared in accordance with Example I, was mixed with Methocel K100LV (hydroxypropyl methylcellulose; Dow Chemicals, MI) in a mixer for 10 minutes.

2. The powder mix from Step 1 was granulated with purified water until a uniform granulation was obtained.

3. The granulation from Step 2 was dried in an oven at 50oC until the moisture content was less than 2% as determined by a loss on drying apparatus operating at 90oC.

4. The dried granulation from Step 3 was milled into a fine powder.

5. The milled granulation from Step 4 was blended with microcrystalline cellulose, talc and magnesium stearate for 5 minutes.

6. The powder blend from Step 5 was compressed into a tablet using a tablet press.

Example IIC

Formulation	% w/w
Amorphous Compound of Formula I	50
Corn Starch	10
Lactose	39
Talc	1

Method of Preparation of Formulation:

1. Amorphous compound of formula I (with a mean particle size of 8 microns as determined by a laser light scattering instrument), which was prepared in accordance with Example I, was mixed with corn starch, lactose and talc for 10 minutes.

2. The powder blend from Step 1 was encapsulated into a capsule.

Example IID

Formulation	% w/w
Amorphous Compound of Formula I	50
Klucel LF	45
Talcum	3
Magnesium Stearate	2

Method of Preparation of Formulation:

1. Amorphous compound of formula I (with a mean particle size of 8 microns as determined by a laser light scattering instrument), which was prepared in accordance with Example I, was mixed with Klucel LF (hydroxypropyl cellulose; Hercules Inc., NJ) in a mixer for 10 minutes.

2. The powder mix from Step 1 was granulated with purified water until a uniform granulation was obtained.

3. The granulation from Step 2 was dried in an oven at 50°C until the moisture content was less than 2% as determined by a loss on drying apparatus operating at 90°C.

4. The dried granulation from Step 3 was milled into a fine powder.

5. The milled granulation from Step 4 was blended with talc and magnesium stearate for 5 minutes.

6. The powder blend from Step 5 was compressed into a tablet using a tablet press.

Example III: Preparation of Pharmaceutical Formulations Including Crystalline Compound of formula I

Example IIIA

Formulation	% w/w
Crystalline Compound of Formula I	50
Lactose Anhydrous	50

Method of Preparation of Formulation: Crystalline compound of formula I (with a mean particle size of 9 microns as determined by a laser light scattering instrument) prepared in accordance with the methods taught in US Patent RE 36,736 was mixed with lactose anhydrous in a mixer for 10 minutes.

Example IIIB

Formulation	% w/w
Crystalline Compound of Formula I (micronized)	4
Methocel K3	4
Purified Water	92

Method of Preparation of Formulation:

1. Methocel K3 (hydroxypropyl methylcellulose; Dow Chemicals, MI) was dispersed in a portion of purified water at a concentration of 20% w/w and mixed well until a uniform dispersion was obtained.

2. Crystalline compound of formula I (with a mean particle size of 5 microns, and prepared in accordance with the methods taught in US Patent RE 36,736) was added to the dispersion from Step 1 and mixed well until a uniform suspension was obtained.

3. The remainder of purified water was added to the suspension from Step 2 and mixed well.

Example IIIC

Formulation	% w/w
Crystalline Compound of Formula I (nanosized)	4
Methocel K3	4
Purified Water	92

Method of Preparation of Formulation:

1. Methocel K3 (hydroxypropyl methylcellulose; Dow Chemicals, MI) was dispersed in purified water at a concentration of 20% w/w and mixed well until a uniform dispersion was obtained.

2. Crystalline compound of formula I (with a mean particle size of 5 microns and prepared in accordance with the methods taught in US Patent RE 36,736) was added to the dispersion from Step 1 and mixed well until a uniform suspension was obtained.

3. The suspension from Step 2 was passed through a DYNOMIL containing glass beads (with mean diameter of 0.2-0.5 mm) as a grinding medium to achieve a mean particle size of compound of formula I in the range of 300-400 nm.

Example IV: Comparison of Physical Properties of Amorphous and Crystalline Compound of Formula I

Various tests were conducted to compare crystalline compound of formula I prepared in accordance with the methods taught in US Patent RE 36,736 with amorphous compound of formula I according to the present invention. Parameters compared include crystallinity, glass transition temperature, dissolution rate and bioavailability. The results of the comparisons are described below and depicted in the accompanying Figures.

As shown in the powder X-ray diffraction pattern in Figure 1, compound of formula I prepared in accordance with the methods taught in US Patent RE 36,736 exhibited distinct crystallinity.

As shown by the powder X-ray diffraction pattern in Figure 2, compound of formula I, which is prepared by the methods taught herein, is distinctly amorphous.

As shown by a differential scanning calorimetry thermogram in Figure 3, compound of formula I prepared in accordance with the methods taught in US Patent RE 36,736 has a distinct endotherm at a temperature of 287°C and is thus crystalline.

As shown by a differential scanning calorimetry thermogram in Figure 4, compound of formula I prepared in accordance with the methods taught herein has a glass transition temperature of approximately 112°C and is thus amorphous.

As shown by the powder X-ray diffraction pattern in Figure 5, amorphous compound of formula I prepared in accordance with the methods taught herein maintained its amorphous properties even under accelerated storage conditions. This means that the compound prepared in accordance with this invention is stable and suitable for incorporation in pharmaceutical formulations.

The formulation of Example IIIA containing crystalline compound of formula I (Example III A) and the formulation of (Example II A) containing amorphous compound of formula I were evaluated for dissolution by a two-stage (two dissolution media) dissolution method. At Stage I, 300 mL of deionized water at 37° ± 0.5°C using paddles at 75 rpm was used. At Stage II, 600 mL of 6% w/v Sodium Lauryl Sulfate in 0.015M Phosphate Buffer, pH 6.8 equilibrated at 37° ± 0.5°C, was carefully added into the

dissolution vessel 25 minutes after the Stage I dissolution was initiated. Sample aliquots were taken at different time intervals and analyzed by UV spectrophotometry.

As shown in Figure 6, the results of the above dissolution evaluation clearly indicate that the dissolution profile of the preparation containing amorphous compound of formula I (Example II A) was faster and more complete than that of the preparation containing crystalline compound of formula I (Example III A).

Additionally, preparations containing crystalline compound of formula I (Examples III B and III C) and amorphous compound of formula I (Example II A) were evaluated for bioavailability in beagle dogs with body weight of approximately 10 kg. Each dog was given a formulation containing 90 mg of compound of formula I. Blood samples were collected from each dog prior to dosing (0 h) and at 0.5, 1, 2, 4, 6, 8, 12, 24, 36 and 48 hours after dosing. EDTA was used as an anticoagulant. Each plasma sample was separated after cold centrifugation and frozen in an amber vial at a minimum of – 60°C before analysis. Compound of formula I was extracted from plasma and the plasma concentration of compound of formula I was determined using a positive ion TurbuIonspray LC-MS/MS assay[HPLC using HP1100 LC system, Hewlett-Packard, Inc. (Agilent Technologies, Wilmington, DE) and Mass Spectrometer using PE-Sciex API-3+ (Perkin-Elmer Instruments, Wilton, CT), Ionization mode: Turbulonspray, 500C, positive ion] The calibration range was 1 to 1,000 ng/mL using a 100-µL plasma sample.

Non-compartmental pharmacokinetic parameters estimated were the maximum plasma concentration (Cmax), the time to reach the Cmax (Tmax), the area under the plasma concentration-time curve ($AUC_{0-\infty}$) from time zero to infinity, dose (mg/kg) normalized Cmax (Cmax/dose) and dose normalized AUC (AUC/dose) for compound of formula I. The observed Cmax and Tmax were taken directly from the concentration-time profile for the individual animal. The $AUC_{0-\infty}$ was calculated using the linear trapezoidal rule by WinNonline™ (Professional Edition version 1.5, Pharsight Corporation, Mountain View, CA).

The results of this bioavailability evaluation are given in Table I below. The data reported in Table I show that the bioavailability in dogs of the compound of formula I in amorphous form (Example IIA) is significantly higher than when the crystalline form of the compound (Examples IIIB and IIIC) is administered to the animals in conventional dosage forms (such as micronized and nanosized suspensions).

Table I: Pharmacokinetics of Compound of Formula I in Dogs[1] after Single Oral Dose Administration (10mg/kg)

Formulation	$AUC_{0-\infty}$/Dose (ng.h/ml)/	T_{max} (hr)	C_{max} (ng/ml)	% Bioavailability[2]
Micronized crystalline compound I suspension (Example III B)	29.5 ± 8.3	1.0 ± 0.0	55 ± 17	4
Nanosized, crystalline compound I suspension (Example IIIC)	86.1 ± 13.7	1.5 ± 0.6	142 ± 53	11
Amorphous compound + Lactose Anhydrous (Example IIA))	468±87	3.4 ± 1.9	874± 452	61
IV Formulation	766±82	N/A[3]	N/A[3]	100

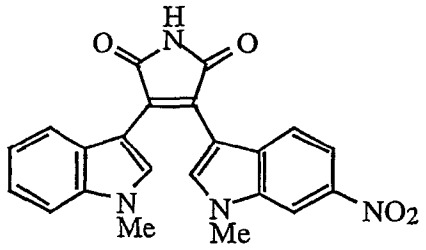
1. N=4, 2 males and 2 females with a parallel design
2. When compared to the IV formulation
3. Not available

While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those skilled in the art that variations may be made without departing from the concept, spirit and scope of the invention.

CLAIMS

We claim:

1. A compound of formula



I

in amorphous form.

2. The compound of claim 1, substantially free of crystalline compound.

3. The compound of claims 1 or 2, wherein the compound is not more than 20% crystalline form.

4. The compound of claims 1 or 2, wherein the compound is not more than 10% crystalline form.

5. A process for the preparation of compound of claim I comprising:

(a) dissolving crystalline compound of formula I in an organic solvent; and

(b) precipitating the desired amorphous compound of formula I from the solution of step (a).

6. The process of claim 5 wherein the organic solvent used in step (a) is selected from the group consisting of ethanol, methanol, acetone, dimethyl sulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone, diethylene glycol ethyl ether, glycofural, propylene carbonate, tetrahydrofuran, polyethylene glycols, and propylene glycols.

7. The process of claim 6 wherein the organic solvent used in step (a) is dimethylacetamide.

8. The process of claim 5 wherein precipitation in step (b) is effected by adding the solution of step (a) to a cold aqueous solution.

9. The process of claim 8 wherein the temperature of the aqueous solution is from about 2°C to about 10 °C.

10. The process of claim 9 wherein the pH of the aqueous solution is one in which the compound of formula I in amorphous form is not soluble.

11. The process of claim 10 wherein the pH of the aqueous solution is from about 2 to about 7.

12. A process for the preparation of compound of claim 1 comprising:

(a) dissolving a compound of formula I in crystalline form in an organic solvent; and

(b) removing the organic solvent.

13. The process of claim 12 wherein the organic solvent is selected from the group consisting of ethanol, methanol, acetone, dimethyl sulfoxide, N, N-dimethylacetamide, N, N-dimethylformamide, N-methylpyrrolidone, diethylene glycol ethyl ether, glycofural, propylene carbonate, tetrahydrofuran, polyethylene glycols, and propylene glycols.

14. The process of claim 12 wherein the organic solvent is removed by spray drying.

15. The process of claim 12 wherein the organic solvent is removed by lyophilization.

16. A process for the preparation of compound of claim 1 comprising:

(a) dissolving a crystalline compound of formula I in a supercritical fluid; and

(b) removing the supercritical fluid.

17. The process of claim 16 wherein the supercritical fluid is liquid nitrogen or liquid carbon dioxide.

18. A process for the preparation of compound of claim 1 comprising:

(a) dissolving a crystalline compound of formula I in an organic solvent; and

(b) extracting the organic solvent from the solution resulting in step (a) with a supercritical fluid as liquid nitrogen or liquid carbon dioxide.

19. A process for the preparation of compound of claim 1, comprising:

(a) continuously exposing a crystalline compound of formula I to a temperature-controlled extruder (hot melt extruder) that is set at different temperature gradients; and

(b) rapidly cooling the extrudate from step (a).

20. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically carrier.

21. The pharmaceutical composition of claim 20 which is free of form stabilizers.

22. The pharmaceutical composition of claim 20 which is free of ionic polymers.

23. A compound of claim 1 when manufactured by a process according to any one of claims 2-16.

24. A method for the treatment of tumors, which method comprises administering a compound according to claims 1 or 2 to a human or an animal.

25. Use of compound according to claims 1 or 2 for the manufacture of a medicament for the treatment of tumors.

26. The novel compound, process, pharmaceutical composition, method and use as described herein.

Powder X-Ray Diffraction Pattern of Crystalline Compound of Formula I

Fig 1.

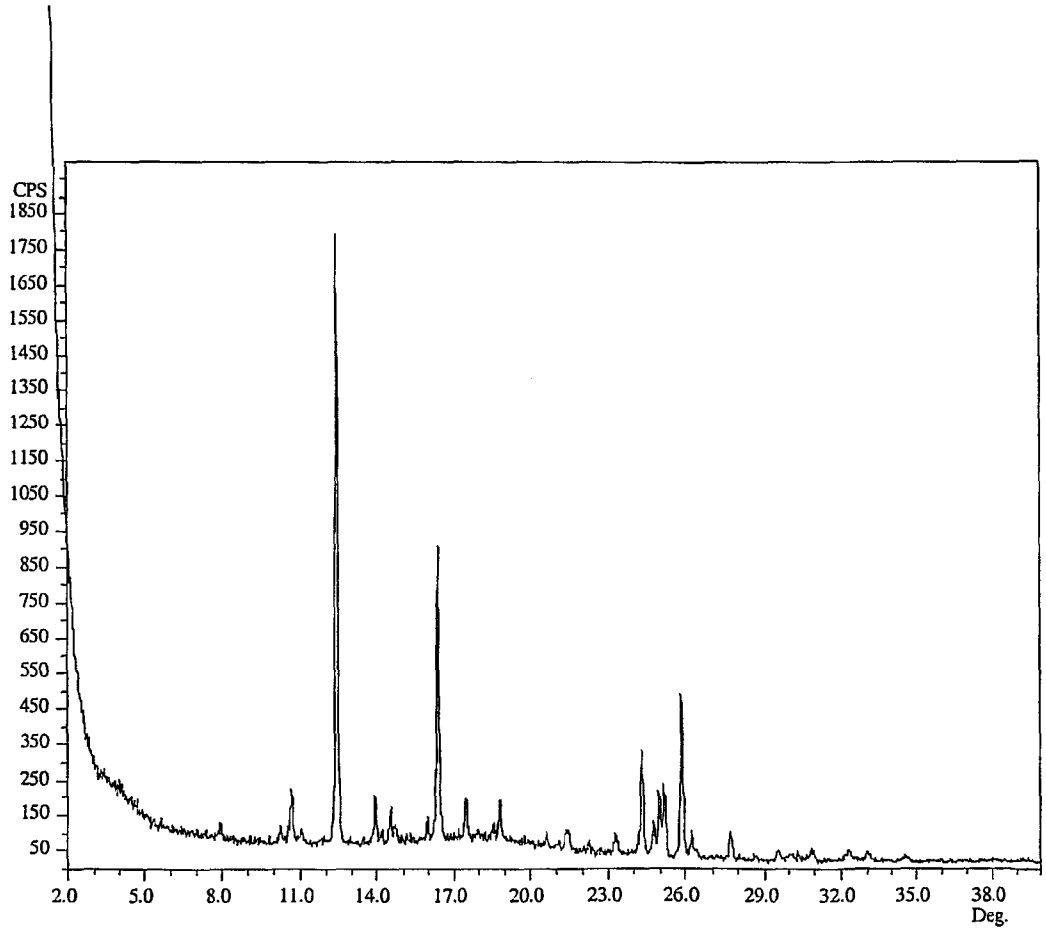


Fig. 2

Powder X-Ray Diffraction Pattern of Compound of Formula I Prepared in Accordance with Invention

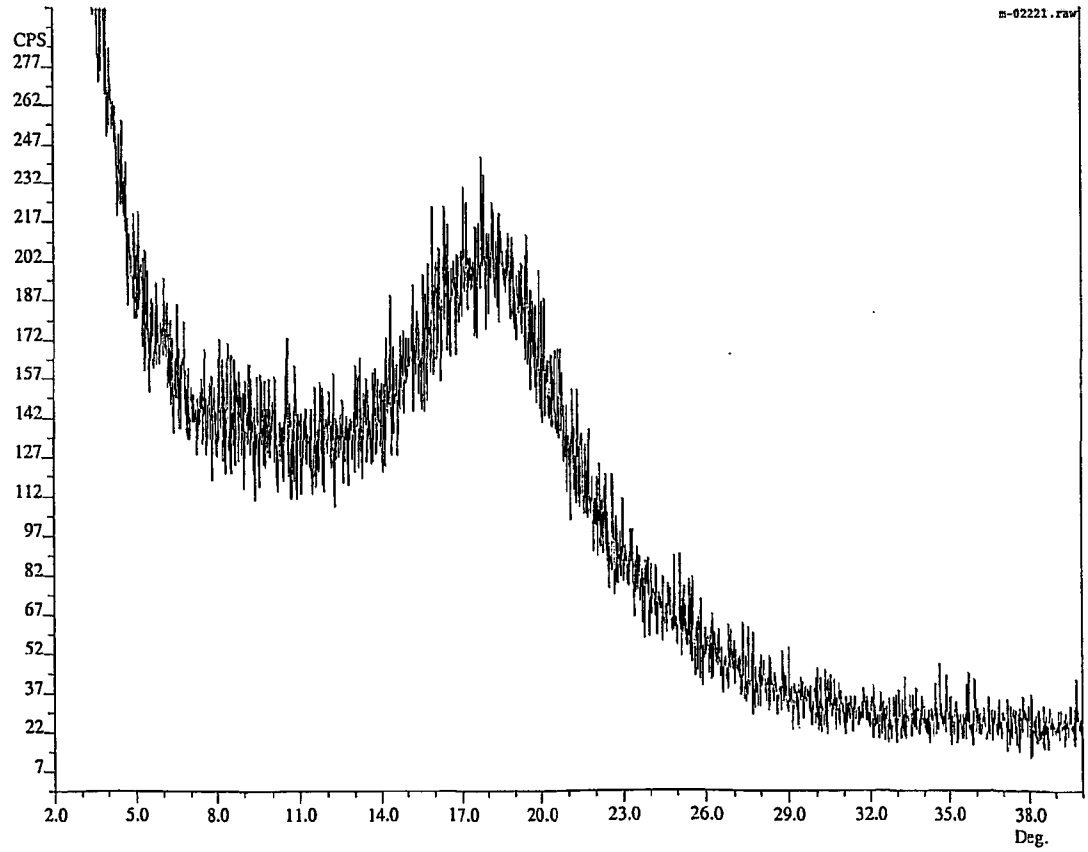


Fig. 3

Differential Scanning Calorimetry Thermogram of Compound of Formula I Prepared According to Known Methods

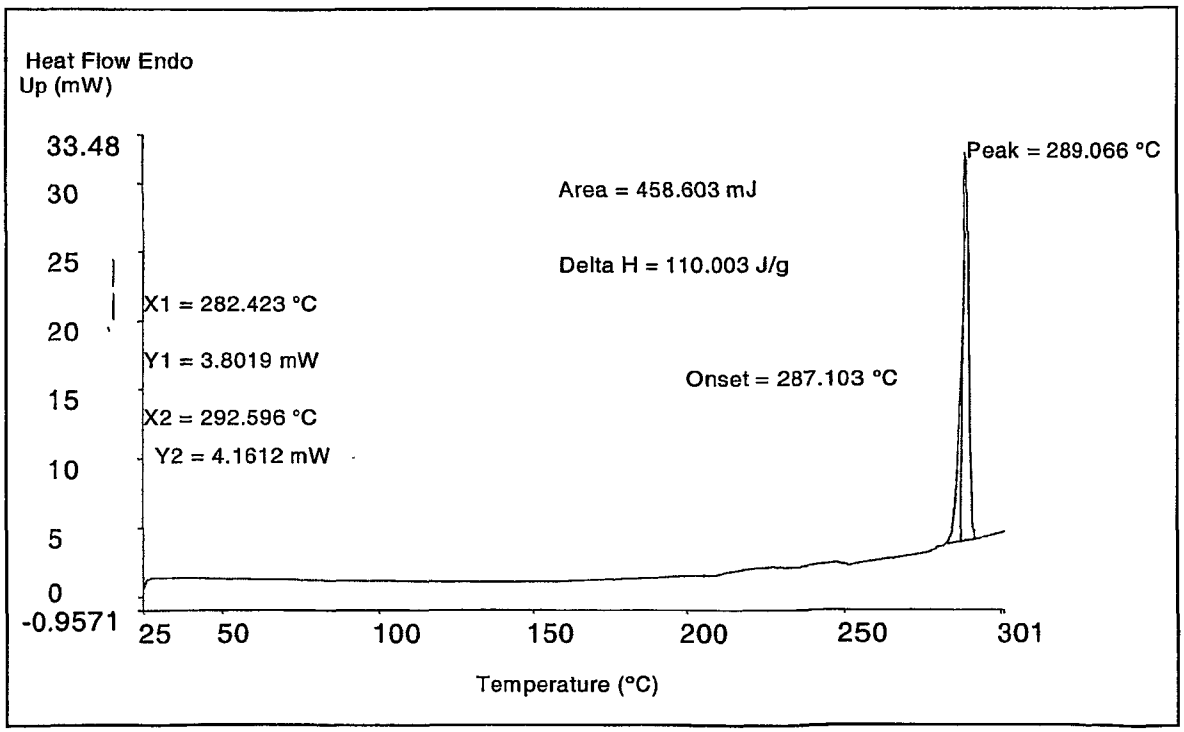


Fig. 4.

Dynamic Differential Scanning Calorimetry Thermogram of Amorphous Compound of Formula I Showing a Glass Transition Temperature of Approximately 112°C

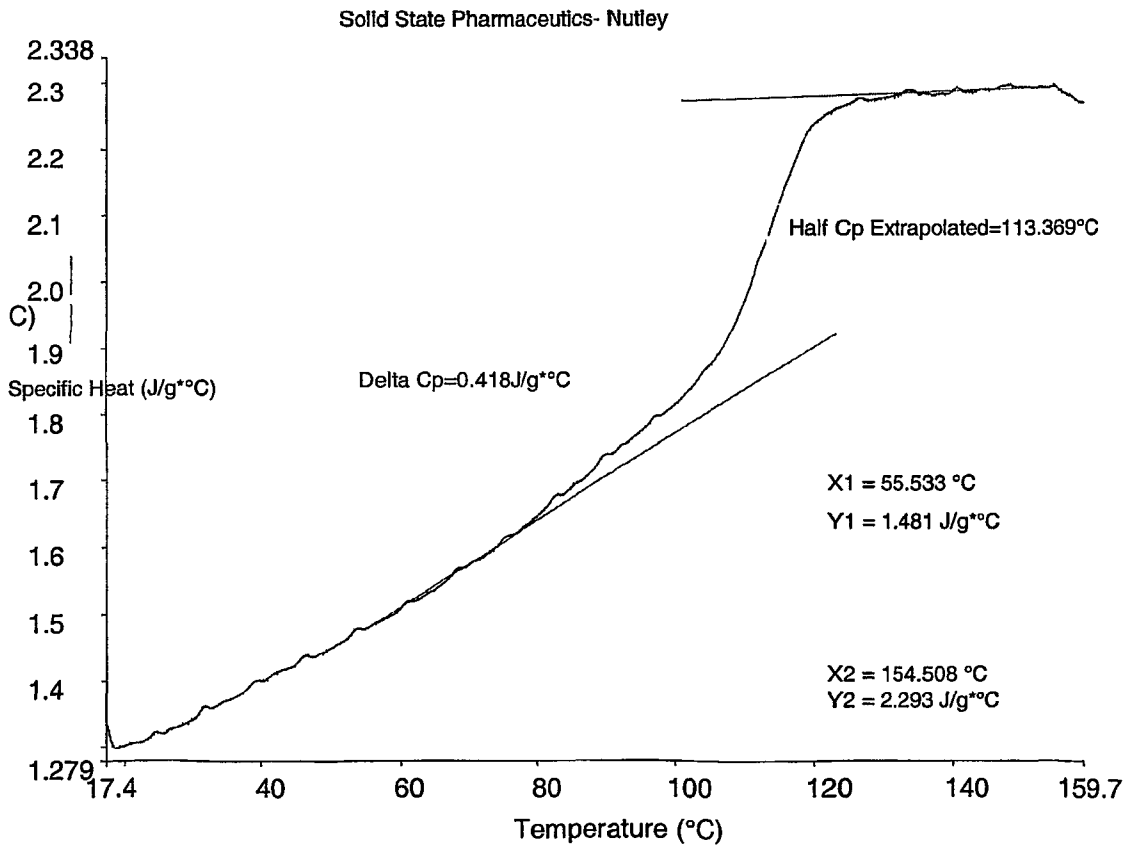


Fig. 5.

Powder X-Ray Diffraction Pattern of High Energy Form of Compound of Formula I After Storage under Accelerated Conditions (40°C/75%RH, 6 months in closed glass vial)

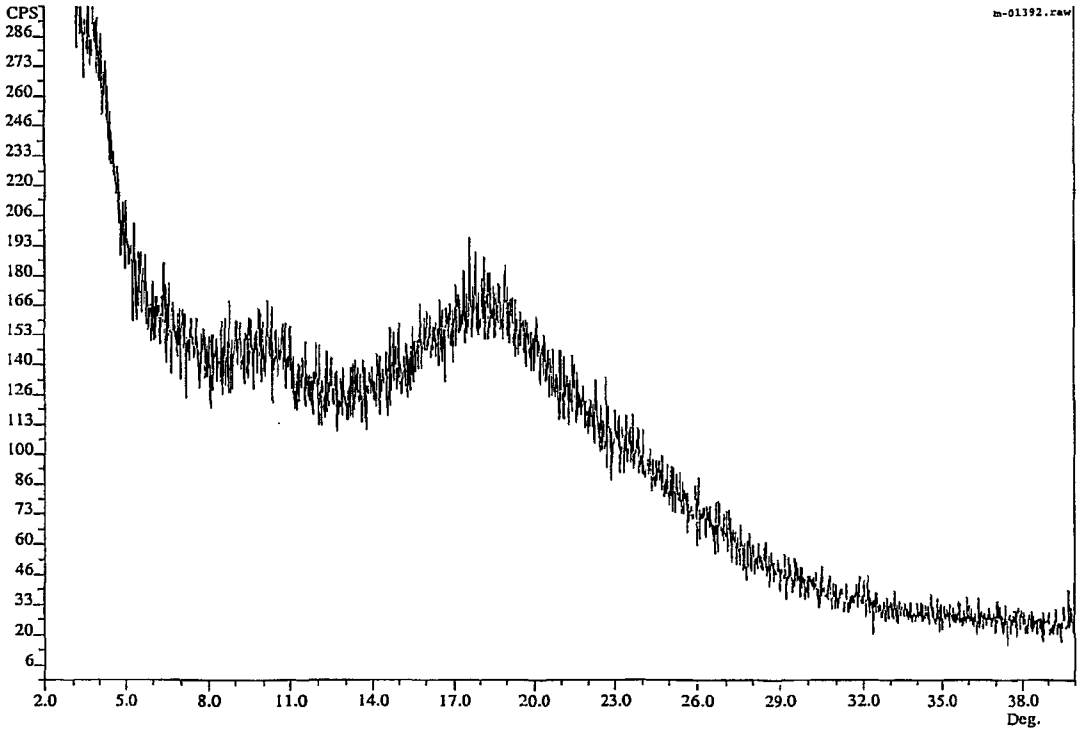


Fig. 6

Dissolution Profiles of Amorphous Compound of Formula I (Produced in Accordance with Example II A) and of Crystalline Compound (Produced in Accordance with Example III A)