TITLE: POLYMORPH FORM OF APREPITANT AND PROCESS FOR THE PREPARATION THEREOF

Abstract: Disclosed herein is a novel stable polymorph of aprepitant, designated polymorph Form III. Also disclosed is a process for its preparation and pharmaceutical compositions containing same.
POLYMORPH FORM OF APREPITANT AND PROCESS FOR THE PREPARATION THEREOF

PRIORITY
[0001] This application claims priority to U.S. Provisional Application No. 60/874,659, filed on December 13, 2006, and entitled "NOVEL POLYMORPH FORM OF APREPITANT AND PROCESS FOR THE PREPARATION THEREOF" and to Indian Provisional Application No. 1690/MUM/2006, filed on October 13, 2006, and entitled "NOVEL CRYSTALLINE FORM OF APREPITANT AND PROCESS FOR THE PREPARATION THEREOF", the contents of each of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION
1. Technical Field
[0002] The present invention generally relates to a novel polymorphic Form of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, also known as aprepitant, process for its preparation, pharmaceutical compositions containing same and a method of treatment of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. The present invention also relates to a process for the preparation of aprepitant in amorphous form.

2. Description of the Related Art
[0003] Aprepitant, also known as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, can be represented by the structure of Formula I:

\[
\text{(I)-} \\
\]
Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NKi) receptors. Aprepitant has little or no affinity for serotonin (5-HT3), dopamine and corticosteroid receptors, which are the targets of some therapies for chemotherapy-induced nausea and vomiting (CINV). Aprepitant, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin and is commercially sold under the trade name Emend®. See, e.g., Physician's Desk Reference. "Emend." 60th Edition, pp. 1944-1949 (2005).


U.S. Patent No. 6,096,742 discloses a polymorphic form of aprepitant characterized by an X-ray powder diffraction pattern with key reflections at approximately: 12.0, 15.3, 16.6, 17.0, 17.6, 19.4, 20.0, 21.9, 23.6, 23.8, and 24.8 degrees (2 theta) which is substantially free of a polymorphic form of aprepitant characterized by an X-ray powder diffraction pattern with key reflections at approximately: 12.6, 16.7, 17.1, 17.2, 18.0, 20.1, 20.6, 21.1, 22.8, 23.9 and 24.8 degrees (2 theta).

U.S. Patent No. 6,583,142 discloses a polymorphic form of aprepitant characterized by an X-ray powder diffraction pattern with key reflections at approximately: 12.6, 16.7, 17.1, 17.2, 18.0, 20.1, 20.6, 21.1, 22.8, 23.9, and 24.8 degrees (2 theta) which is substantially free of a polymorphic form of aprepitant characterized by an X-ray powder diffraction pattern with key reflections at approximately: 12.0, 15.3, 16.6, 17.0, 17.6, 19.4, 20.0, 21.9, 23.6, 23.8, and 24.8 degree (2 theta).

Morphological forms of pharmaceutical compounds may be of interest to those involved in the development of a suitable dosage form because if the morphological form is not held constant during clinical and stability studies, the exact dosage used or measured may not be comparable from one lot to the next. Once a pharmaceutical compound is produces for use, it is important to recognize the morphological form delivered in each dosage form to assure that the production processes use the same form and that the same amount of drug is included in each dosage. Therefore, it is imperative to assure that either a single morphological form or some known combination of morphological forms is present. In addition, certain morphological forms may exhibit...
enhanced thermodynamic stability and may be more suitable than other morphological forms for inclusion in pharmaceutical formulations. As used herein, a polymorphic form of a chemical compound is the same chemical entity, but in a different crystalline arrangement.

[0008] The difference in the physical properties of different morphological forms results from the orientation and intermolecular interactions of adjacent molecules are complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantages physical properties compared to other crystalline forms of the same compound or complex. The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It also adds to the material 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 characteristic. A new polymorphic form of aprepitant has now been discovered.

SUMMARY OF THE INVENTION
[0009] In accordance with one embodiment of the present invention, aprepitant in polymorph Form III is provided.
[0010] In accordance with a second embodiment of the present invention, aprepitant in polymorph Form III and having an X-ray diffraction (XRD) pattern substantially in accordance with Figure 1 is provided.
[0011] In accordance with a third embodiment of the present invention, aprepitant in polymorph Form III and having a differential scanning calorimetric thermogram substantially in accordance with Figure 2 is provided.
[0012] In accordance with a fourth embodiment of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of aprepitant in polymorph Form III.
[0013] In accordance with a fifth embodiment of the present invention, a process for preparing aprepitant in polymorph Form III is provided comprising (a) providing a suspension of aprepitant in one or more solvents capable of suspending aprepitant; and (b)
substantially removing the solvent from the suspension to provide aprepitant in polymorph Form III.

[0014] In accordance with a sixth embodiment of the present invention, a process for preparing aprepitant in an amorphous form is provided comprising (a) providing a solution of aprepitant in one or more solvents capable of dissolving aprepitant; and (b) recovering aprepitant in the amorphous form from the solution by substantially removing the solvent.

DEFINITIONS
[0015] The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0016] The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0017] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

[0018] The term "buffering agent" as used herein is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds

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include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such material known to those of ordinary skill in the art.

[0019] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0020] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Such compounds include, by way of example and without limitation, acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch, combinations thereof and other material known to those of ordinary skill in the art.

[0021] When needed, other binders may also be included in the present invention. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and other such materials known to those of ordinary skill in the art.

[0022] The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.
The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "lubricant" as used herein is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "disintegrant" as used herein is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pregelatinized and modified starched thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g. Avicel™), carsium (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "wetting agent" as used herein is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol,
polyvinylpyrrolidone (PVP), tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton), combinations thereof and other such materials known to those of ordinary skill in the art.

Most of these excipients are described in detail in, e.g., Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), which are incorporated by reference herein.

The polymorphic form of aprepitant of the present invention is believed to be advantageous over other known forms of aprepitant in terms of thermodynamic stability and suitability for inclusion in pharmaceutical formulations.

BREIF DESCRIPTION OF THE DRAWING

Figure 1 is a characteristic powder X-ray diffraction (XRD) pattern of aprepitant in polymorph Form III.

Figure 2 is a characteristic Raman Spectra of aprepitant in polymorph Form III.

Figure 3 is a characteristic differential scanning calorimetric (DSC) thermogram of aprepitant in polymorph Form III.

Figure 4 is a characteristic XRD pattern of aprepitant in amorphous form.

detailed description of the invention

One embodiment of the present invention is directed to a novel polymorph form of aprepitant, designated polymorph Form III. The novel polymorph Form III of aprepitant may be characterized by, for example, X-ray powder diffraction pattern and/or melting point. The XRD pattern for aprepitant in polymorph Form III is presented in Figure 1. In one embodiment, the present invention provides aprepitant in polymorph Form III characterized as having characteristic peaks (expressed in degrees 20 ± 0.2°θ) at approximately one or more of the positions: about 9.6 and about 10.5. In another embodiment, the present invention provides aprepitant in polymorph Form III characterized as having characteristic peaks (expressed in degrees 20 ± 0.2°θ) at
approximately one or more of the positions: about 6.9, about 7.5, about 9.6 and about 10.5.

In yet another embodiment, the present invention provides aprepitant in polymorph Form III characterized as having characteristic peaks (expressed in degrees 20 ± 0.2°θ) at approximately one or more of the positions: about 6.9, about 7.5, about 9.6, about 10.5, about 13.5, about 14.8, about 17.4, about 20.1, and about 23.1.

[0034] In another embodiment, aprepitant in polymorph Form III can be characterized by having at least one, and preferably all, of the following properties: (a) an XRD substantially in accordance with Figure 1; and/or (b) a Raman spectrum substantially in accordance with Figure 2; and/or (c) a DSC substantially in accordance with Figure 3.

[0035] Aprepitant in polymorph Form III can be obtained by at least:

(a) providing a suspension comprising aprepitant in one or more solvents capable of suspending aprepitant; and

(b) substantially removing the solvent from the solution to provide aprepitant in polymorph Form III.

[0036] Step (a) of the process for preparing aprepitant in polymorph Form III of the present invention may include adding aprepitant to a suitable solvent or obtaining an existing solution or suspension from a previous processing step. The starting aprepitant used in the present invention may be any crystalline or other form of aprepitant, including various solvates, hydrates and salts, known in the art and can be prepared by known techniques. Examples of salts that may be used with the present invention include sodium, calcium, potassium, acetate, benzoate, fumarate, maleate, citrate, tartrate, hydrochloride and hydrobromide salts. With crystallization processes, the crystalline form of the starting material does not usually affect the final result since the original crystalline form is lost once a material goes into solution.

[0037] Suitable solvents include, but are not limited to, alcoholic solvents having from 1 to 12 carbon atoms, halogenated solvents, aromatic hydrocarbon solvents, non-aromatic hydrocarbon solvents and the like and mixtures thereof. Preferably, the solvent is a mixture of halogenated solvents and alcohol solvents. Generally, the mixture will contain the solvents in a ratio of halogenated solvents to alcohol solvents ranging from about 40:about 60.
Useful alcoholic solvents include methanol, ethanol, isopropanol, butanol and the like and mixtures thereof.

Useful halogenated solvents include dichloromethane, ethylene dichloride, chloroform, carbon tetrachloride and the like and mixtures thereof.

Useful aromatic hydrocarbons include benzene, toluene, xylene and the like and mixtures thereof.

Useful non-aromatic hydrocarbons include hexane, heptane and the like and mixtures thereof.

The aprepitant can be added to the solvent at an elevated temperature, e.g., a temperature ranging from about 20°C to about 65°C, preferably from about 40°C to about 50°C, and most preferably at about 47°C. The suspension can optionally be filtered to remove any extraneous matter present in the suspension using any standard filtration techniques known in the art.

Step (b) of the process for preparing aprepitant in polymorph Form III of the present invention includes removing the solvent from the suspension by cooling the suspension for a time period sufficient to form aprepitant in polymorph Form III from the suspension. The aprepitant in polymorph Form III can then be isolated from the suspension by techniques known in the art, e.g., filtration. The resulting material can then be dried at a suitable temperature.

The resulting polymorph Form III of aprepitant of the present invention can be obtained in relatively high purity, e.g., a purity greater than or equal to about 96%, preferably greater than or equal to about 99%, and more preferably greater than or equal to about 99.5% or more as measured by HPLC.

Another embodiment of the present invention is directed to a preparation for preparing an amorphous form of aprepitant. The XRD pattern of the amorphous form of aprepitant of the present invention is substantially in accordance with Figure 4. The amorphous form of aprepitant can be obtained by at least (a) providing a solution of aprepitant in one or more solvents capable of dissolving aprepitant; and (b) recovering aprepitant in the amorphous form from the solution by substantially removing the solvent.

In step (a) of this process of the present invention, a solution of aprepitant can be prepared by dissolving any form of aprepitant in a suitable solvent or obtaining an
existing solution from a previous processing step. Suitable solvents include, but not limited to, one or more lower alkanols, ether-containing solvents, ester-containing solvents, ketone-containing solvents, polar aprotic solvents, water, and the like and mixtures thereof. Suitable lower alkanols include one or more of primary, secondary and tertiary alcohol having from 1 to about 12 carbon atoms such as, for example, methanol, ethanol, n-propanol, isopropanol, t-butanol and the like and mixtures thereof.

[0047] In step (b) of this process of the present invention, the solvent can be removed by techniques known in the art, e.g., distillation, distillation under vacuum, evaporation, freeze-drying, lyophilization, filtration, filtration under vacuum, recantation, centrifugation, etc. Preferably, aprepitant in an amorphous form is recovered from the solution by freeze-drying.

[0048] The amorphous form of aprepitant was stored under various solvent atmospheres and at different relative humidity (RH) conditions as generally set forth below in Table 1.

<table>
<thead>
<tr>
<th>Solvent Vapors</th>
<th>Humidity Conditions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>11 (LiCl·H₂O)</td>
</tr>
<tr>
<td>EtOH</td>
<td>33 (MgCl₂·6H₂O)</td>
</tr>
<tr>
<td>IPA</td>
<td>62 (NH₄NO₃)</td>
</tr>
<tr>
<td>MEK</td>
<td>92 (KNO₃)</td>
</tr>
</tbody>
</table>

All amorphous samples stored under an organic solvent environment were found to crystallize rapidly.

[0049] In one embodiment, the novel polymorph Form III of aprepitant and/or amorphous form of aprepitant disclosed herein for use in the preparation of pharmaceutically acceptable salts or pharmaceutical compositions of the present invention can have a D₅₀ and D₉₀ particle size of less than about 400 microns, preferably less than about 200 microns, more preferably less than about 100 microns, still more preferably less than about 10 microns and most preferably less than about 5 microns. It is noted the notation Dₓ means that X% of the particles have a diameter less than a specified diameter.
D. Thus, a D$_{50}$ of about 400 microns means that 50% of the micronized particles in a composition have a diameter less than about 400 microns. The term "micronization" used herein means any process or methods by which the size of the particles is reduced. The particle sizes can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state novel polymorph Form III of aprepitant and/or amorphous form of aprepitant disclosed herein into any of the foregoing desired particle size range.

[0050] Yet another aspect of the present invention is directed to the pharmaceutical compositions containing the novel polymorph Form III of aprepitant and/or amorphous form of aprepitant as disclosed herein. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, and rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The dosage forms may contain the novel polymorph Form III of aprepitant and/or amorphous form of aprepitant disclosed herein as is or, alternatively, may contain the novel polymorph Form III of aprepitant and/or amorphous form of aprepitant disclosed herein as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field, e.g., the buffering agents, sweetening agents, binders, diluents, fillers, lubricants, wetting agents and disintegrants described herein above.

[0051] Capsule dosages will contain the novel polymorphic Form III of aprepitant and/or amorphous form of aprepitant of the present invention within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings containing at least phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be
employed with suitable plasticizers and/or extending agents. A coated capsule or tablet
may have a coating on the surface thereof or may be a capsule or tablet comprising a
powder or granules with an enteric-coating.

[0052] A composition for tableting or capsule filing can be prepared by wet
granulation. In wet granulation, some or all of the active ingredients and excipients in
powder form are blended and then further mixed in the presence of a liquid, typically
water, which causes the powders to clump up into granules. The granulate is screened
and/or milled, dried and then screened and/or milled to the desired particle size. The
granulate can then be tableted or other excipients can be added prior to tableting, such as a
glidant and/or a lubricant.

[0053] A tableting composition can also be prepared conventionally by dry
blending. For example, the blended composition of the actives and excipients can be
compacted into a slug or a sheet and then comminuted into compacted granules. The
compacted granules can be compressed subsequently into a tablet. As an alternative to dry
granulation, a blended composition can be compressed directly into a compacted dosage
form using direct compression techniques. Direct compression produces a more uniform
tablet without granules.

[0054] Tableting compositions may have few or many components depending
upon the tableting method used, the release rate desired and other factors. For example,
the compositions of the present invention may contain diluents such as cellulose-derived
materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl
cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose,
hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and
unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium
carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the
art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like
mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and
gelatin.

[0055] Other excipients contemplated by the present invention include binders,
such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used
in wet and dry granulation and direct compression tableting processes; disintegrants such
as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

[0056] Actual dosage levels of the novel polymorphic Form III of aprepitant and/or amorphous form of aprepitant disclosed herein may be varied to obtain an amount that is effective to obtain a desired therapeutic response for a particular composition and method of administration for treatment of a mammal. The selected dosage level therefore depends upon such factors as, for example, the desired therapeutic effect, the route of administration, the desired duration of treatment, and other factors. The total daily dose of the novel polymorph administered to a host in single or divided dose and can vary widely depending upon a variety of factors including, for example, the body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs, the severity of the particular condition being treated, etc.

[0057] The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

[0058] CHARACTERIZATION:

[0059] 1. Polarized Optical Microscopy
[0060] The crystal habit of the material was determined using an Olympus RX50 polarized optical microscope equipped with a high resolution JVC camera and image capture software. All images were recorded at 100X magnifications.

[0061] 2. Raman Spectroscopy
[0062] All analyses were performed on a Nicolet Almega Dispersive Raman using a 780nm diode laser operating at 100% power. The Raman spectra were recorded from 98-3917 cm⁻¹ with a typical resolution of 10-19 cm⁻¹. All analyses were performed in duplicate.
3. Differential Scanning Calorimetry

Approximately 1-5 mg of sample was accurately weighed into an aluminum DSC pan with lid. The sample was then placed into a Pyris Diamond DSC (Perkin-Elmer) equipped with a liquid nitrogen cooling unit and allowed to equilibrate at 25°C until a stable heat flow response was seen. A dry helium purge gas at a flow rate of 20 ml/min was used to produce an inert atmosphere and prevent oxidation of the sample during heating. The sample was then scanned from -10°C to 300°C at a scan rate of 200°C/min and the resulting heat flow response (mW) measured against temperature. Prior to experimental analysis the instrument was temperature and heat-flow calibrated using indium as reference standard.

4. X-Ray Powder Diffraction (XRPD)

Approximately 30 mg of sample was gently compressed on the XRPD zero back ground single obliquely cut silica sample holder. The sample was then loaded into a Philips X-Pert MPD diffractometer and analysed using the following experimental conditions.

- Tube anode: Cu
- Generator tension: 40 kV
- Tube current: 40 mA
- Wavelength alpal: 1.5406 Å
- Wavelength alpha2: 1.5444 Å
- Start angle [2θ]: 5
- End angle [2θ]: 50
- Time per step: 2.5 seconds
- Scan step size: 0.02

EXAMPLE 1

Preparation of Polymorph Form III of Aprepitant

Aprepitant (50 mg) was suspended in a mixture of 2 ml of chloroform:ethanol (40:60) and the suspension was stored at 47°C for 30 minutes with agitation. The suspension was filtered through a 0.45 μm syringe filter and the resultant
solution stored at -20°C for 14 days. After such time, the crystalline material was separated from the solvent and the sample dried under vacuum for 24 hours.

[0078] The XRD, Raman Spectra and DSC of the final product are set forth in Figures 1-3 and was recorded and identified as aprepitant in polymorph Form III.

EXAMPLE 2

[0079] Preparation of Amorphous Form of Aprepitant

[0080] Aprepitant (250 mg) was dissolved in t-butanol (50 ml) and the sample was filtered through a 0.45 µm PTFE syringe filter. The solution was added dropwise to liquid nitrogen and the sample was freeze dried.

[0081] The XRD of the final product is set forth in Figure 4 and was recorded and identified as aprepetant in an amorphous form.

[0082] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.
WHAT IS CLAIMED IS:

1. Aprepitant in polymorph Form III.

2. The aprepitant in polymorph Form III of Claim 1, having a powder X-ray diffraction (XRD) pattern comprising characteristic peaks (expressed in degrees $2\theta \pm 0.2^\circ$) at one or more of the positions: about 9.6 and about 10.5.

3. The aprepitant in polymorph Form III of Claim 1, having a powder XRD pattern comprising characteristic peaks (expressed in degrees $2\theta \pm 0.2^\circ$) at approximately one or more of the positions: about 6.9, about 7.5, about 9.6 and about 10.5.

4. The aprepitant in polymorph Form III of Claim 1, having a powder XRD pattern comprising characteristic peaks (expressed in degrees $2\theta \pm 0.2^\circ$) at approximately one or more of the positions: about 6.9, about 7.5, about 9.6, about 10.5, about 13.5, about 14.8, about 17.4, about 20.1, and about 23.1.

5. The aprepitant in polymorph Form III of Claims 1-4, characterized by a XRD pattern substantially in accordance with Figure 1.

6. The aprepitant in polymorph Form III of Claims 1-5, characterized by a Raman spectrum substantially in accordance with Figure 2.

7. The aprepitant in polymorph Form III of Claims 1-6, characterized by a differential scanning calorimetric thermogram substantially in accordance with Figure 3.

8. The aprepitant in polymorph Form III of Claims 1-7, having a purity of greater than or equal to about 99% as measured by HPLC.

9. A pharmaceutical composition comprising a therapeutically effective amount of aprepitant in polymorph Form III according to any one of Claims 1-8.
10. The pharmaceutical composition of Claim 9, further comprising one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants.

11. The pharmaceutical composition of Claims 9 and 10, which is in a solid form.

12. The pharmaceutical composition of Claims 9-11, in a form of a tablet, caplet, capsule, suspension, troche or powder.

13. The pharmaceutical composition of Claims 9-12, wherein the aprepitant in polymorph Form III is micronized aprepitant in polymorph Form III having a particle size distribution equal to or less than about 50 microns.

14. The pharmaceutical composition of Claims 9-12, wherein the aprepitant in polymorph Form III is micronized aprepitant in polymorph Form III having a particle size distribution equal to or less than about 15 microns.

15. A process for preparing aprepitant in polymorph Form III according to any one of Claims 1-8, the process comprising (a) heating a suspension comprising aprepitant in a solvent selected from the group consisting of a halogenated hydrocarbon, an alcohol and mixtures thereof; and (b) cooling and isolating aprepitant in polymorph Form III.

16. The process of Claim 15, wherein the solvent is a mixture of a halogenated hydrocarbon and an alcohol.

17. The process of Claims 15 and 16, wherein the solvent is a mixture of a halogenated hydrocarbon and an alcohol in a ratio of halogenated hydrocarbon to alcohol of about 40:about 60.

18. The process of Claim 15, wherein the solvent is a mixture of chloroform and ethanol.
19. The process of Claims 15 and 16, wherein the solvent is a mixture of chloroform and ethanol in a ratio of chloroform to ethanol of about 40:about 60.

20. The process of Claims 15-19, wherein the suspension of step (a) is heated to a temperature of about 20°C to about 65°C.

21. The process of Claims 15-19, wherein the solution of step (a) is heated to a temperature of about 40°C to about 50°C.

22. The process of Claims 15-19, wherein the solution of step (a) is heated to a temperature of about 47°C.

23. The process of Claims 15-22, wherein the step of cooling comprises cooling the solution for a time period sufficient to form aprepitant in polymorph Form III.

24. The process of Claims 15-23, wherein aprepitant in polymorph Form III is isolated by filtration.

25. The process of Claims 15-24, wherein the isolated aprepitant in polymorph Form III is dried.

26. The use of aprepitant in polymorph Form III according to any one of Claims 1-8 in the manufacture of a medicament for use in the treatment or prevention of emesis in a mammal.

27. A method for the treatment or prevention of emesis in a mammal in need thereof which comprises administering to the mammal an effective amount of the polymorphic form of Claims 1-8.
28. A process for preparing aprepitant in an amorphous form, the process comprising:
   (a) providing a solution of aprepitant in one or more solvents capable of dissolving
       the aprepitant; and
   (b) freeze drying the solution to provide amorphous aprepitant.

29. The process of Claim 28, wherein the solvent comprises one or more alcoholic
    solvent having from 1 to 12 carbon atoms.

30. The process of Claims 28 and 29, wherein the solvent is t-butanol.
### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** C07D413/06 A61K31/5377

According to International Patent Classification (IPC) or both national classification and IPC:

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched:

Electronic database consulted during the international search (name of database and, where practical, search terms used)

- EPO-Internal
- EMBASE
- BIOSIS
- WPI Data
- BEILSTEIN Data
- CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of actual completion of the international search: 15 October 2007

Date of mailing of the international search report: 1st. 01. 2008

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31/70) 340-3016

Authorized officer: Frel on, D. Dier
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.  [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2.  [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3.  [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4.  [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   see additional sheet(s)

Remark on Protest  

   [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

   [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

   [ ] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27
   Polymorph Form III of aprepitant
   ---

2. claims: 28-30
   Process for the preparation of amorphous aprepitant
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## INTERNATIONAL SEARCH REPORT

### Information on patent family members

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Form PCT/ISA/210 (patent family annex) (April 2005)