Abstract:
The present invention relates to new crystalline compounds containing Trigonelline and a cocrystal former. More particularly the present invention relates to Trigonelline cocrystals, therapeutic uses of the Trigonelline cocrystals and pharmaceutical compositions containing them. The cocrystal formers of the present invention include ascorbic acid, L-arginine, aspirin, caffeine, caffeic acid, carnitine, Chlorogenic acid, chrysanth, creatine, coumaric acid, curcumin, EGCG, ferulic acid, gallic acid, genistein, glucosamine HCl, 4-hydroxybenzoic acid, 4-hydroxyisoleucine, ibuprofen, lipoic acid, luteolin, melatonin, MSM, naproxen, naringenin, naringin, nicotinamide, nicotinic acid, paracetamol, protocatechuic acid, L-proline, Quercetin, rutin, resveratrol.
COCRYSTALS OF TRIGONELLINE

FIELD OF THE INVENTION

The present invention relates to new crystalline compounds containing Trigoneline and a cocrystal former. More particularly the present invention relates to Trigonelline cocrystals, therapeutic uses of the Trigoneline cocrystals and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Trigonelline is an alkaloid. It is a zwitterion formed by the methylation of nitrogen atom of Niacin (Vitamin B₃). Trigonelline is a product of nicacin metabolism having the following structure

\[
\begin{align*}
\text{OH} & \\
\text{C} & \\
\text{N} & \\
\text{CH₃} &
\end{align*}
\]

Trigonelline occurs in many plants. It has been isolated from fenugreek seeds (Trigonella foenum-graecum, hence the name), garden peas, hemp seed, oats, potatoes, Stachys species, dahlia, Strophanthus species and Dichapetalum cymosum., Holtz, Kutscher and Theilmann have recorded its presence in a number of animals.

Trigonelline is also found in coffee. Higher levels of trigonelline is found in arabica coffee.

Trigonelline crystallizes as a monohydrate from alcohol in hygroscopic prisms (m.p. 130 °C or 218 °C. It is readily soluble in water or warm alcohol, less so in cold alcohol, and slightly so in chloroform or ether. The salts crystallize well, the monohydrochloride, in leaflets, sparingly soluble in dry alcohol. The picrate forms shining prisms (m.p. 198-200 °C) soluble in water but sparingly soluble in dry alcohol or ether.

The trigonelline in coffee is the precursor of NMP (n-methylium pyridine) which is currently reported as a diabetes active principle in WO 2010/055170 A1.
Trigonelline is further known in cosmetic applications, as disclosed in DE 3915535 Al.

WO 2010/054818 A1 discloses a method of preparation a NMP-containing extract starting with roasting trigonelline containing plant material (as e.g. coffee,). The roasted trigonelline containing organic material is then treated with water to obtain an aqueous extract. The latter is then treated with polyamide and subjected to cation exchange chromatography to obtain a NMP-containing extract. Due to the use of polyamide this production method is not exclusively natural.

US 8,772,230 B2 discloses the use of niacin and/ or trigonelline compounds to increase muscle weight during periods of activity or to inhibit muscle loss during periods of inactivity.

US 7,141,254 B2 discloses a synergistic composition for the treatment of diabetes in a subject in need thereof, said composition-comprising Trigonelline of concentration ranging between 20 to 30%, amino acids of concentration ranging between 20 to 60%, and soluble fibre of concentration ranging between 10 to 60%, optionally along with pharmaceutically acceptable additives, a process thereof and also, a method of treating diabetes.

Though a number of pharmacological studies have been conducted on Trigonelline, but, very little investigation on the behaviour of Trigonelline in the solid state has appeared in the open literature, and thus its solid-state properties appear not to have been thoroughly studied to date.

Cocrystals have generated tremendous interest in pharmaceutical research and development because of the potential to customize physicochemical properties of the solid while maintaining the chemical integrity of the drug. Cocrystals are part of a broader class of multicomponent crystals, where two or more molecules (commonly referred to as drug and coformer) populate a homogeneous crystalline lattice in a welldefined stoichiometry. What distinguishes cocrystals from other types of multicomponent crystals such as salts and solvates is that drug and coformer are solids at ambient temperature and that the intermolecular interactions are nonionic in nature. The diversity of solid forms that can be generated from a drug greatly increases through cocrystallization; the physicochemical properties of the cocrystals can vary depending on the characteristics of its constituent molecules. Pharmaceutically relevant properties that can change via cocrystallization include but are not limited to solubility, dissolution, moisture uptake, chemical stability, mechanical properties, and bioavailability. Of these properties, solubility is the most widely appreciated...
in the literature. Cocrystals have the potential to address the solubility limitations of poorly soluble pharmaceutical compounds, a problem which can pose a serious challenge to successful formulation.

The main advantage of cocrystals is the ability to generate a variety of solid forms of a drug that have physicochemical properties distinct from the solid cocrystal components. Such properties include but are not limited to solubility, dissolution, bioavailability, hygroscopicity, hydrate/solvate formation, crystal morphology, fusion properties, chemical and thermal stability, and mechanical properties. These properties can directly or indirectly affect the suitability of a particular API as a pharmaceutical product.

A cocrystal of a drug (an active nutraceutical ingredient or an active pharmaceutical ingredient) is a distinct chemical composition between the drug and coformer, and generally possesses distinct crystallographic and spectroscopic properties when compared to those of the drug and coformer individually. Unlike salts, which possess a neutral net charge, but which are comprised of charge-balanced components, cocrystals are comprised of neutral species. Thus, unlike a salt, one cannot determine the stoichiometry of a cocrystal based on charge balance. Indeed, one can often obtain cocrystals having stoichiometric ratios of drug to coformer of greater than or less than 1:1. The stoichiometric ratio of an API to coformer is a generally unpredictable feature of a cocrystal.

To the best of the inventors' knowledge, no cocrystals of Trigonelline have been reported in the open/academic or patent literature. In fact, the field of pharmaceuticals and nutraceuticals cocrystals appears to be a relatively unexplored landscape.

**OBJECTIVES OF THE INVENTION**

The main object of the present invention is to provide Trigonelline cocrystals.

Another object of the present invention is to provide cocrystals of Trigonelline with enhanced bioavailability.

Still another object of the present invention is to provide cocrystal of Trigonelline with Epigallocatechin gallate (EGCG).

Still another objective of the present invention is to provide cocrystal of Trigonelline with chloregenic acid.

Still another objective of the present invention is to provide cocrystal of Trigonelline with Quercetin.
Still another objective of the present invention is to provide cocrystal of Trigonelline with 4-hydroxyisoleucine.

Still another objective of the present invention is to provide a process for the preparation of the Trigonelline cocrystals.

Further objective of the present invention is to provide compositions of cocrystal of Trigonelline.

Further objective of the present invention is to provide pharmaceutical dosage forms of Trigonelline cocrystal.

SUMMARY OF THE INVENTION

Accordingly, the present invention relates to novel cocrystals of Trigonelline with a cocrystal former.

In another embodiment the present invention specifically relates to cocrystal of Trigonelline with Epigallocatechin gallate (EGCG) ("Cocrystal 1").

In yet another embodiment the present invention specifically relates to cocrystal of Trigonelline with Chloregenic acid ("Cocrystal 2").

In still another embodiment the present invention specifically relates to cocrystal of Trigonelline with Quercetin ("Cocrystal 3").

In yet another embodiment the present invention specifically relates to cocrystal of Trigonelline with 4-Hydroxyisoleucine ("Cocrystal 4").

Methods of making the Trigonelline cocrystals are a further aspect of the present invention.

In an aspect of the present invention provides processes for the preparation of cocrystals of Trigonelline comprising mixing Trigonelline and a cocrystal former optionally in the presence of an organic solvent or water.

In an aspect of the present invention provides processes for the preparation of cocrystals of Trigonelline comprising milling Trigonelline and a cocrystal former.

In an aspect of the present invention provides processes for the preparation of cocrystals of Trigonelline comprising melting a mixture of Trigonelline and a cocrystal former optionally in the presence of an organic solvent or water.

In an aspect of the present invention provides processes for the preparation of cocrystals of Trigonelline comprising providing a solution of a mixture of Trigonelline and a cocrystal former in an organic solvent or water optionally seeding with co-crystals of Trigonelline and forming cocrystals.
In an aspect, the present invention provides processes for the preparation of co-crystals of Trigonelline, comprising Trigonelline and a co-crystal former, an embodiment including providing a solution comprising Trigonelline and a co-crystal former in a solvent, and combining an anti-solvent with the solution.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the XRPD pattern of Trigonelline : Epigallocatechin gallate (EGCG) co-crystal.

Figure 2 shows ¹H NMR of Trigonelline : Epigallocatechin gallate (EGCG) co-crystal.

Figure 3 shows DSC of Trigonelline : Epigallocatechin gallate (EGCG) co-crystal.

Figure 4 shows TGA of Trigonelline : Epigallocatechin gallate (EGCG) co-crystal.

Figure 5 shows the solid state stability of Trigonelline : Epigallocatechin gallate (EGCG) co-crystal at ambient temperature normal packed condition (bottom) and after 6 months (top).

Figure 6 shows the XRPD pattern of Trigonelline : Chlorogenic acid co-crystal.

Figure 7 shows ¹H NMR of Trigonelline : Chlorogenic acid co-crystal.

Figure 8 shows DSC of Trigonelline : Chlorogenic acid co-crystal.

Figure 9 shows TGA of Trigonelline : Chlorogenic acid co-crystal.

Figure 10 shows the solid state stability of Trigonelline : Chlorogenic acid crystal at ambient temperature normal packed condition (bottom) and after 6 months (top).

Figure 11 shows the XRPD pattern of Trigonelline : Quercetin. co-crystal.

Figure 12 shows ¹H NMR of Trigonelline : Quercetin. co-crystal.

Figure 13 shows DSC of Trigonelline : Quercetin. co-crystal.

Figure 14 shows TGA of Trigonelline : Quercetin. co-crystal.

Figure 15 shows the solid state stability of Trigonelline : Quercetin co-crystal at ambient temperature normal packed condition (bottom) and after 6 months (top).

Figure 16 shows the XRPD pattern of Trigonelline : 4-hydroxyisoleucine co-crystal.

Figure 17 shows ¹H NMR of Trigonelline : 4-hydroxyisoleucine co-crystal.

Figure 18 shows DSC of Trigonelline : 4-hydroxyisoleucine co-crystal.

Figure 19 shows TGA of Trigonelline : 4-hydroxyisoleucine co-crystal.

Figure 20 shows the solid state stability of Trigonelline : 4-hydroxyisoleucine co-crystal at ambient temperature normal packed condition (bottom) and after 6 months (top).

DETAILED DESCRIPTION OF THE INVENTION
Aspects of the present invention relates to cocrystal, comprising Trigonelline and a cocrystal former, and processes for preparation thereof.

As used herein, the term "co-crystal" denotes crystalline molecular complexes, encompassing hydrates and solvates. "Co-crystals" are composed of multi-component, stoichiometric and neutral molecular species, each existing as a solid under ambient conditions.

Co-crystals exhibit properties different from free drugs or salts. The solid form influences relevant physico-chemical parameters such as solubility, dissolution rate of the drug, chemical stability, melting point, and hygroscopicity, which can result in solids with superior properties.

As used herein the cocrystal formers of the present invention include, but are not limited to ascorbic acid, L-arginine, aspirin, caffeine, caffeic acid, carnitine, Chlorogenic acid, chrysin, creatine, coumaric acid, curcumin, EGCG, ferulic acid, gallic acid, genistein, glucosamine HCl, 4-hydroxybenzoic acid, 4-hydroxyisoleucine, ibuprofen, lipoic acid, luteolin, melatonin, MSM, naproxen, naringenin, naringin, nicotinamide, nicotinic acid, paracetamol, protocatecuic acid, L-proline, Quercetin, rutin, resveratrol.

Useful cocrystal formers of the present invention specifically include, EGCG, Chlorogenic acid, Quercetin, 4-hydroxyisoleucine.

The molecular structures of the Coctystal former specifically used according to the present invention are shown below:
The invention relates to novel Trigonelline cocrystals with Epigallocatechin gallate (EGCG) designated as cocrystal 1. Chlorogenic acid designated as cocrystal 2, Quercetin designated as cocrystal 3 and 4-hydroxyisoleucine cocrystal 4.

The above cocrystals were prepared by employing the appropriate process techniques. The process consists of dissolving Epigallocatechin gallate (ECGG) in water at ambient temperature. After clear solution is obtained, Trigonelline hydrate was added to the clear solution for almost 3 and half hours. After completion of the reaction, the reaction mixture is filtered and the solid obtained was evaluated for PXRD, DSC, TGA, Proton NMR and stability testing.


The obtained Trigonelline : Epigallocatechin (EGCG) cocrystal is also confirmed by proton NMR (Fig 2).

The obtained Trigonelline : Epigallocatechin gallate cocrystal is further characterized by a DSC curve having an endotherm peaks at 67, 19 °C and at 101.19 °C (Fig 3).

The obtained Trigonelline : Epigallocatechin gallate cocrystal is also characterized by a TGA curve corresponding to a weight loss of less than about 11.75 % (Fig 4).

The obtained Trigonelline : Epigallocatechin gallate cocrystal was subject to stability testing at ambient temperature for six months. The inventors have observed that the cocrystal remains stable wherein they observed no changes in the PXRD pattern (PXRD) without loss of crystallinity (Fig 5). Moreover, the solid maintains its good handling properties.

The Trigonelline : chlorogenic acid cocrystas is prepared by dissolving Trigonelline hydrate in methanol at ambient temperature. To the resulting clear solution was added
stoichiometric chlorogenic acid and slurried for 1 hr and 30 minutes. The obtained solid was filtered, dried and subjected to analytical tests.


The obtained Trigonelline : Chlorogenic acid cocrystal is also confirmed by proton NMR (Fig 7).

The obtained Trigonelline : chlorogenic acid cocrystal is further characterized by a DSC curve having an endothermic peak at 129.74 °C (Fig 8).

The obtained Trigonelline : chlorogenic acid cocrystal is also characterized by a TGA curve corresponding to a weight loss of less than about 3.972 % (Fig 9).

The obtained Trigonelline : chlorogenic acid cocrystal was subjected to stability testing at ambient temperature for six months. The inventors have observed that the cocrystal remains stable wherein they observed no changes in the PXRD pattern without loss of crystallinity (Fig 10). Moreover, the solid maintains its good handling properties.

The Trigonelline :Quercetin cocrystals is prepared by dissolving Trigonelline hydrate in methanol at ambient temperature. To the resulting clear solution was added stoichiometric Quercetin dihydrate and slurried for 5hrs. The obtained solid was filtered, dried and subjected to analytical tests.


The obtained Trigonelline : Quercetin cocrystal is also confirmed by proton NMR (Fig 12).

The obtained Trigonelline : Quercetin cocrystal is further characterized by a DSC curve having an endotherm peaks at 148.60 °C and 214.66 °C (Fig 13).

The obtained Trigonelline : Quercetin cocrystal is also characterized by a TGA curve corresponding to a weight loss of less than about 7.086 % (Fig 14).
The obtained Trigonelline : Quercetin cocrystal was subjected to stability testing at ambient temperature for six months. The inventors have observed that the cocrystal remains stable wherein they observed no changes in the PXRD pattern without loss of crystallinity (Fig 15). Moreover, the solid maintains its good handling properties.

The Trigonelline 4-hydroxyisoleucine cocrystals is prepared by dissolving 4-hydroxyisoleucine in stoichiometric amount of water at ambient temperature. The obtained clear solution acetone as anti-solvent was added and the slurry was stirred for 6 hrs. After completion of the reaction, the obtained solid was filtered, dried and subjected to analytical tests.


The obtained Trigonelline : 4-hydroxyisoleucine cocrystal is also confirmed by proton NMR (Fig 17).

The obtained Trigonelline : 4-hydroxyisoleucine cocrystal is further characterized by a DSC curve having an endothermic peak at 201.89 °C (Fig 18).

The obtained Trigonelline : 4-hydroxyisoleucine cocrystal is also characterized by a TGA curve corresponding to a weight loss of less than about 6.377 %. (Fig 19)

The obtained Trigonelline : 4-hydroxyisoleucine cocrystal was subjected to stability testing at ambient temperature for six months. The inventors have observed that the cocrystal remains stable wherein they observed no changes in the PXRD pattern without loss of crystallinity (Fig 20). Moreover, the solid maintains its good handling properties.

These Trigonelline cocrystals of the present invention are used to improve the physicochemical and biopharmaceutical properties of pharmaceutical and nutraceutical ingredients.

These co-crystals exhibit highly unexpected and exceptional properties. This is in sharp contrast to the formation of different crystalline forms of a substance for which it is possible at least to predict the existence by means of proper software.

The above mentioned four co-crystals of Trigonelline described above, according to our knowledge, have never been disclosed in the prior art. Indeed, it is believed that there are no co-crystals of Trigonelline disclosed in literature for its purification. Thus, the preparation
of Trigonelline co-crystals is an exceptional and unexpected event, especially considering that Trigonelline itself has been known for many years and many studies relating to its preparation have been carried out resulting in large volumes of related literature.

An important advantage of methods according to the present invention is that further steps for purification of the co-crystal in order to reach the purity level necessary for the preparation of Trigonelline of pharmaceutical grade are not required.

Organic solvents that may be used for preparation of the co-crystals of the present invention include, but are not limited to: water; alcohols such as methanol, ethanol, 1-propanol, 1-butanol, 2-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, 2-ethoxyethanol, ethylene glycol, glycerol, and the like; ketones such as acetone, butanone, 2-pentanone, 3-pentanone, methyl butyl ketone, methyl iso-butyl ketone, and the like; esters such as ethyl formate, methyl acetate, ethyl acetate, propyl acetate, t-butyl acetate, isobutyl acetate, methyl propanoate, ethyl proponoate, methyl butanoate, ethyl butanoate, and the like; ethers such as diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, 2-methoxyethanol, 2-ethoxyethanol, anisole, and the like; aliphatic and alicyclic hydrocarbons, unsubstituted and substituted, such as hexanes, n-heptane, n-pentane, cyclohexane, methylcyclohexane, nitromethane, and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, and the like; aromatic hydrocarbons such as toluene, xylenes, chlorobenzene, tetraline, and the like; nitriles such as acetonitrile, propionitrile, and the like; and any mixtures thereof.

The dissolution may be carried out at temperatures suitable for complete dissolution of the components, without affecting its quality.

Any physical form of Trigonelline, such as crystalline, amorphous, and their mixtures may be utilized for providing the solution.

Suitable anti-solvents that may be used include, but are not limited to: ethers such as diethyl ether, dimethyl ether, diisopropylether, tetrahydrofuran, 1,4-dioxane, and the like; hydrocarbons such as n-hexane, n-heptane, cyclohexane, toluene, xylene, acetone and the like; and mixtures thereof.

The anti-solvent may be added to the solution comprising Trigonelline and a co-crystal former at temperatures ranging from about 20°C to about 60°C, or at room temperature.

Illustrative examples of certain analytical data for the co-crystals of Trigonelline obtained in the examples are set forth in Figures 1-20.
In another embodiment, the present invention provides pharmaceutical compositions comprising cocrystals of Trigonelline, together with one or more pharmaceutically acceptable excipients.

The pharmaceutical compositions comprising co-crystals of Trigonelline may be further formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using procedures such as direct blending, dry granulation, wet granulation, or extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present application may further comprise one or more pharmaceutically acceptable excipients that find use in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches, and the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodiums, colloidal silicon dioxide, and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethyl celluloses, methyl celluloses, various grades of methyl methacrylates, waxes, and the like. Other pharmaceutically acceptable excipients that are of use include, but are not limited to, film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, and the like.
Certain specific aspects and embodiments of the present invention will be explained in more detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the invention in any manner.

The following Examples will further illustrate the present invention, which by no means limit the scope of the invention.

**Example 1**

Trigonelline Epigallocatechin gallate (EGCG) cocrystal (1:1)

500 mg (1.091 mmol) 92% of ECGG was dissolved in 1.1 ml of water at ambient temperature. To this clear solution 169.21 mg (1.091 mmol) of Trigonelline hydrate was added and the slurry stirred for 3 hrs and 30 minutes. The obtained mass was filtered and dried under vacuum to give the title compound.

**Example 2**

Trigonelline Chlorogenic acid cocrystal (1:1)

200 mg (1.29 mmol) of Trigonelline hydrate was dissolved in 1 ml of methanol at ambient temperature. To this clear solution 530 mg (1.46 mmol) of chlorogenic acid was added and the slurry was stirred for 1 hr and 30 minutes. The obtained mass was filtered and dried under vacuum to give the title compound.

**Example 3**

Trigonelline Quercetin Cocrystal (1:1)

155 mg (1 mmol) of Trigonelline hydrate was dissolved in 4 ml of methanol at ambient temperature. To this clear solution 338 mg (1 mmol) of Quercetin dihydrate was added and the slurry was stirred for 5 hrs. The resulting wet solid was filtered, dried under vacuum to give the title compound.

**Example 4**

Trigonelline 4-hydroxyisoleucine cocrystal (1:1)

330 mg (2.24 mmol) of 4-hydroxyisoleucine and 316.3 mg (2.04 mmol) Trigonelline hydrate were dissolved in 2.4 ml of water at ambient temperature. To this clear solution acetone (antisolvent) was added and the slurry stirred for 6 hrs. The resulting wet cake was filtered and dried under vacuum to give the title compound.
We claim,

1. Novel cocrystals of Trigonelline with a cocrystal former.

2. The cocrystals of Trigonelline as claimed in claim 1 wherein the cocrystal formers is selected from ascorbic acid, L-arginine, aspirin, caffeine, caffeic acid, carnitine, Chlorogenic acid, chrysin, creatine, coumaric acid, curcumin, EGCG, ferulic acid, gallic acid, genistein, glucosamine HCl, 4-hydroxybenzoic acid, 4-hydroxyisoleucine, ibuprofen, lipoic acid, luteolin, melatonin, MSM, naproxen, naringenin, naringin, nicotinamide, nicotinic acid, paracetamol, protocatecuic acid, L-proline, Quercetin, rutin, resveratrol.

3. The cocrystals of Trigonelline as claimed in claim 1 wherein the cocrystal is of Trigonelline with Epigallocatechin gallate (EGCG) ("Cocrystal 1").

4. The cocrystals of Trigonelline as claimed in claim 1 wherein the cocrystal is of Trigonelline with Chlorogenic acid ("Cocrystal 2").

5. The cocrystals of Trigonelline as claimed in claim 1 wherein the cocrystal is of Trigonelline with Quercetin ("Cocrystal 3").

6. The cocrystals of Trigonelline as claimed in claim 1 wherein the cocrystal is of Trigonelline with 4-Hydroxyisoleucine ("Cocrystal 4").

7. The cocrystals of Trigonelline as claimed in claim 1 prepared by a process comprising
   a. milling Trigonelline and a cocrystal former or
   b. melting a mixture of Trigonelline and a cocrystal former optionally in the presence of an organic solvent or water or
   c. providing a solution of a mixture of Trigonelline and a cocrystal former in an organic solvent or water optionally seeding with co-crystals of Trigonelline and forming cocrystals or
   d. providing a solution comprising Trigonelline and a co-crystal former in a solvent, and combining an anti-solvent with the solution.

The Trigonelline: Epigallocatechin gallate cocrystal (ECGG) as claimed in claim 3, characterized by DSC curve having an endotherm peaks at 67.19 °C and at 101.19 °C.


The Trigonelline: chlorogenic acid cocrystal as claimed in claim 4, characterized by DSC curve having an endotherm peak at 129.74 °C.


The Trigonelline: Quercetin cocrystals as claimed in claim 5, characterized by DSC curve having an endothermic peaks at 148.60 °C and 214.66 °C.


The Trigonelline: 4-hydroxyisoleucine cocrystal as claimed in claim 6, characterized by DSC curve having an endothermic peak at 201.89 °C.

A composition comprising: an amount of cocrystals of Trigonelline and one or more excipients.
Figure 3
Figure 4

Weight (%) vs Temp

Temperature:
- 79.48°C
- 180.07°C

Weight (%):
- 11.78%
- 0.7083%
Figure- 5
Figure 8

![Graph showing heat flow vs. temperature with peaks at 117.25°C and 128.74°C.](image-url)
Figure 12
Figure 13

A graph showing the heat flow (W/g) as a function of temperature (°C). The graph includes several temperature peaks and valleys with specific values indicated. For example, a peak at 138.32°C with a heat flow of 0.31 W/g, and another at 221.53°C with 46.25 W/g.
Figure 18

Heat Flow (mJ/g)

Temperature (°C)

71.52°C
135.73 g
96.00°C
220.60°C
425.43 g
251.89°C
Figure 20

2Theta (Coupled TwoTheta/Theta) WL=1.54080
A. CLASSIFICATION OF SUBJECT MATTER
A61K31/455 Version=2016.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/455

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
24-10-2016

Date of mailing of the international search report
24-10-2016

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