(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 January 2021 (14.01.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/005545 A1

(51) International Patent Classification:
C07D 273/04 (2006.01)

(21) International Application Number:
PCT/IB2020/056457

(22) International Filing Date:
09 July 2020 (09.07.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201921027683 10 July 2019 (10.07.2019) IN

(71) Applicant: **GHARDA CHEMICALS LIMITED** [IN/IN]; D-1/2, MIDC, Lote Parshuram, Taluka Khed, Ratnagiri-, Maharashtra 415722 (IN).

(72) Inventors: **GHARDA, Keki Hormusji**; Gharda Chemicals Limited, 48, Hill Road, Bandra West, Mumbai-, Maharashtra 400050 (IN). **SHENOY, Diwakar K**; c/o Gharda Chemicals Limited, D-1/2, MIDC, Lote Parshuram, Taluka Khed, Ratnagiri-, Maharashtra 415722 (IN). **SHET, Laxminarayan S**; c/o Gharda Chemicals Limited, D-1/2, MIDC, Lote Parshuram, Taluka Khed, Ratnagiri-, Maharashtra 415722 (IN). **SAMANGADKAR, Yatin S**; c/o Gharda Chemicals Limited, D-1/2, MIDC, Lote Parshuram, Taluka Khed, Ratnagiri-, Maharashtra 415722 (IN). **SALVI, Manoj V**; c/o Gharda Chemicals Limited, D-1/2, MIDC, Lote Parshuram, Taluka Khed, Ratnagiri-, Maharashtra 415722 (IN).

(74) Agent: **DEWAN, Mohan**; R. K. Dewan & Co. Podar Chambers, S. A. Brelvi Road, Fort, Mumbai-, Maharashtra 400001 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) **Title:** A PROCESS FOR OBTAINING INDOXACARB CRYSTALS WITH SPECIFIC PURITY AND ENANTIOMERIC RATIO

(57) **Abstract:** The present disclosure relates to a process for obtaining an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%, wherein the enantiomeric mixture comprises crystals of R-isomer and S-isomer. The S-isomer crystals are present in an amount in the range of 75% to 90% of the enantiomeric mixture. The raw material used is crude Indoxacarb comprising impurities in an amount in the range of 10 wt.% to 15 wt.%. The process of the present disclosure is simple, economical, gives relatively high purity of Indoxacarb crystals than crude Indoxacarb and avoids deterioration in the amount of the active S-isomer.

WO 2021/005545 A1

A PROCESS FOR OBTAINING INDOXACARB CRYSTALS WITH SPECIFIC PURITY AND ENANTIOMERIC RATIO

FIELD

The present disclosure relates to a process for obtaining Indoxacarb crystals with specific purity and specific enantiomeric ratio.

DEFINITION

As used in the present disclosure, the following terms are generally intended to have the meaning as set forth below, except to the extent that the context in which they are used indicate otherwise.

Equilibration refers to a process of allowing an enantiomeric solution to attain equilibrium, for obtaining a specific enantiomeric ratio.

Crude Indoxacarb refers to Indoxacarb obtained from a manufacturing unit, comprising optically active isomer of Indoxacarb (S-isomer) and optically inactive isomer of Indoxacarb (R-isomer) along with impurities. Crude Indoxacarb is either amorphous or crystalline in nature. The impurities are inert in nature comprising compounds such as oxadiazine precursor, oil, solvent and the like. The amount of impurities present in crude Indoxacarb is in the range of 10 wt. % to 15 wt.%.

BACKGROUND

The background information herein below relates to the present disclosure but is not necessarily prior art.

Indoxacarb is an oxadiazine compound with pesticidal activity, especially effective against lepidopteran larvae. Crude Indoxacarb can be either in amorphous form or in crystalline form. The crystalline form of Indoxacarb exhibits improved properties and stability in formulations as compared to the amorphous form, wherein the latter has a greater tendency to aggregate. However, the process of obtaining a crystalline form with high purity is tedious and expensive.

Further, the insecticidal activity of Indoxacarb is mainly attributed to the (+)-S-isomer whereas the R-isomer is inactive. However, it is difficult to control the desired ratio of the S-isomer by using the conventional methods. Further, the purification process for improving the purity of the crystalline form may lead to deterioration in the amount of the S-isomer.

Therefore, there is felt a need, for an efficient process for obtaining Indoxacarb crystals with specific purity, without deterioration of the active S-isomer.

OBJECTS

Some of the objects of the present disclosure, which at least one embodiment herein satisfies, are as follows.

It is an object of the present disclosure to ameliorate one or more problems of the prior art or to at least provide a useful alternative.

Another object of the present disclosure is to provide Indoxacarb crystals having specific purity and specific enantiomeric ratio.

Still another object of the present disclosure is to provide an efficient process for obtaining Indoxacarb crystals with specific purity without any deterioration in the amount of the S-isomer.

Other objects and advantages of the present disclosure will be more apparent from the following description, which is not intended to limit the scope of the present disclosure.

SUMMARY

The present disclosure provides a process for obtaining an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%. The process comprises mixing crude Indoxacarb with a solvent to obtain a slurry, wherein the crude Indoxacarb comprises impurities in an amount in the range of 10 wt.% to 15 wt.%. The slurry is heated to a temperature in the range of 74 °C to 85 °C to obtain a heated slurry. The heated slurry is cooled to a temperature in the range of 55 °C to 70 °C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. At least one portion of the warm slurry is filtered at a temperature in the range of 55 °C to 70 °C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The filtrate is mixed with

the remaining portion of the warm slurry to obtain a first mixture. The first mixture is cooled to a temperature in the range of 10 °C to 25 °C to initiate crystallization followed by equilibrating under stirring for a time period in the range of 3 hours to 8 hours to allow complete crystallization to obtain a second mixture containing enantiomeric crystals of Indoxacarb comprising R-isomer and S-isomer of Indoxacarb. The second mixture is filtered to separate the enantiomeric crystals of Indoxacarb. The crystals are washed and dried to obtain an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%; wherein said enantiomeric mixture of Indoxacarb comprises crystals of R-isomer and S-isomer, wherein the S-isomer crystals are present in an amount in the range of 75% to 90% of said enantiomeric mixture.

Crude Indoxacarb comprises an enantiomeric mixture containing crystals of R-isomer and S-isomer, wherein the crystals of S-isomer are present in an amount of at least 70% of the enantiomeric mixture.

In another aspect, the present disclosure provides an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%. The enantiomeric mixture comprise crystals of R-isomer and S-isomer of Indoxacarb. The S-isomer crystals are present in an amount in the range of 75 % to 90% of the enantiomeric mixture.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWING

The present disclosure will now be described with the help of the accompanying drawing, in which:

Figure 1 illustrates Differential scanning calorimetry (DSC) graph of sample 1A (racemic mixture), in accordance with the process of the present disclosure;

Figure 2 illustrates Differential scanning calorimetry (DSC) graph of sample 2A, in accordance with the process of the present disclosure;

Figure 3 illustrates X-Ray Diffraction (XRD) data of sample 1A (racemic mixture), in accordance with the process of the present disclosure; and

Figure 4 illustrates X-Ray Diffraction (XRD) data of sample 2A (mixture of R and S isomers of Indoxacarb), in accordance with the process of the present disclosure.

DETAILED DESCRIPTION

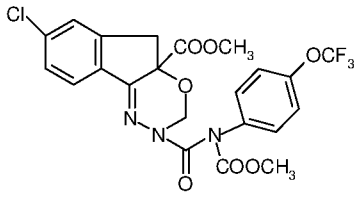
Embodiments, of the present disclosure, will now be described with reference to the accompanying drawing.

Embodiments are provided so as to thoroughly and fully convey the scope of the present disclosure to the person skilled in the art. Numerous details, are set forth, relating to specific components, and methods, to provide a complete understanding of embodiments of the present disclosure. It will be apparent to the person skilled in the art that the details provided in the embodiments should not be construed to limit the scope of the present disclosure. In some embodiments, well-known processes, well-known apparatus structures, and well-known techniques are not described in detail.

The terminology used, in the present disclosure, is only for the purpose of explaining a particular embodiment and such terminology shall not be considered to limit the scope of the present disclosure. As used in the present disclosure, the forms "a," "an," and "the" may be intended to include the plural forms as well, unless the context clearly suggests otherwise. The terms "comprises," "comprising," "including," and "having," are open ended transitional phrases and therefore specify the presence of stated features, integers, steps, operations, elements, modules, units and/or components, but do not forbid the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. The particular order of steps disclosed in the method and process of the present disclosure is not to be construed as necessarily requiring their performance as described or illustrated. It is also to be understood that additional or alternative steps may be employed.

The terms first, second, third, etc., should not be construed to limit the scope of the present disclosure as the aforementioned terms may be only used to distinguish one element, component, region, layer or section from another component, region, layer or section. Terms such as first, second, third etc., when used herein do not imply a specific sequence or order unless clearly suggested by the present disclosure.

Indoxacarb (I) is an important pesticidal compound, having oxadiazine as the structural unit and a single chiral center. Indoxacarb shows improved properties in its crystalline form than in the amorphous form.



(I)

The insecticidal activity of Indoxacarb is mainly attributed to the (+)-S-isomer whereas the R-isomer is inactive. Conventional processes of obtaining crystalline Indoxacarb lead to a mixture of R-isomer and S-isomer, and further purification would lead to the deterioration in the amount of the S-isomer, thus reducing the overall activity, as the S-isomer is the active component.

The present disclosure provides a simple and effective process for preparing Indoxacarb crystals having a specific purity and a specific enantiomeric ratio. The process enhances the purity of Indoxacarb, with the same or relatively higher amount of S-isomer than that in the crude Indoxacarb.

In one aspect, the present disclosure provides a process for obtaining an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%. The process is described in detail herein below.

Crude Indoxacarb is mixed with a solvent to obtain a slurry. The crude Indoxacarb comprises impurities in an amount in the range of 10 wt.% to 15 wt.%. In an embodiment, the crude Indoxacarb has purity in the range of 70% to 90%.

Crude Indoxacarb, obtained from a manufacturing unit, comprises optically active isomer of Indoxacarb (S-isomer) and optically inactive isomer of Indoxacarb (R-isomer) along with impurities. The impurities are inert in nature comprising compounds such as oxadiazine precursor, oil, solvent. The amount of impurities in crude Indoxacarb are in an amount in the range of 10 wt. % to 15 wt.%. Crude Indoxacarb is either amorphous or crystalline in nature.

Crude Indoxacarb comprises an enantiomeric mixture containing crystals of R-isomer and S-isomer, wherein the crystals of S-isomer are present in an amount of at least 70% of the enantiomeric mixture. In an embodiment, the crystals of S-isomer in crude Indoxacarb are present in an amount of 75% of the enantiomeric mixture.

In an embodiment, the crude Indoxacarb is obtained in an amorphous lump form.

In an embodiment of the present disclosure, the crude Indoxacarb has purity of 86%. In another embodiment, the crude Indoxacarb has purity of 88%.

In an exemplary embodiment, the crude Indoxacarb has impurity of 13 wt.%.

In accordance with the present disclosure, the solvent is selected from aliphatic alcohols with C_1 to C_{10} carbon atoms and cyclic alcohols.

Typically, the solvent is selected from the group consisting of methanol, ethanol, 2-propanol, 1-butanol and cyclohexanol. In an exemplary embodiment, the solvent is 2-propanol.

The weight-volume ratio of crude Indoxacarb and the solvent in the mixing step is in the range of 1:0.8 to 1:1.5. In an embodiment, the weight-volume ratio of crude Indoxacarb and the solvent is 1:1.

The weight-volume ratio value lesser than 1:0.8 would lead to insufficient solubility whereas a ratio greater than 1:1.5 would lead to the use of excess solvent which not only leads to wastage but also affects the recrystallization of R-isomers and S-isomers during equilibration, resulting in comparatively lesser recovery.

In an embodiment, the impurities are mainly inert impurities that get dissolved by the solvent at room temperature.

Further, the slurry is heated to a temperature in the range of 74 °C to 85 °C to obtain a heated slurry. Typically, the slurry is heated to a temperature in the range of 74 °C to 76 °C. In an exemplary embodiment, the solvent used is 2-propanol and the slurry is heated to 75 °C.

The heating of the slurry in the temperature range of 74 °C to 85 °C ensures better separation of racemic Indoxacarb in the heated slurry. This range of temperature is important because below 70 °C, separation of racemic Indoxacarb will be ineffective and above 85 °C, there might be loss of solvent in the slurry due to evaporation, depending upon the solvent used.

In the next step, the heated slurry is cooled to a temperature in the range of 55 °C to 70 °C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb.

The racemic Indoxacarb has lower solubility than the enantiomeric Indoxacarb and hence crystallizes out partially in the cooling step. The removal of racemic Indoxacarb ensures that the inactive R-isomer is relatively reduced and the amount of S-isomer in the final composition is relatively higher than in the crude Indoxacarb.

Typically, the heated slurry is cooled to a temperature in the range of 60 °C to 70 °C. In an embodiment, the heated slurry is cooled to 65 °C.

In the next step, at least one portion of the warm slurry is filtered at a temperature in the range of 55 °C to 70 °C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate.

The at least one portion of the warm slurry is in the range of 10 vol.% to 20 vol.%. In an embodiment, 15 vol.% of the warm slurry is filtered.

In an exemplary embodiment, the warm slurry is cooled to 65 °C and the filtration is done at 65 °C.

Further, the filtrate is mixed with the remaining portion of the warm slurry to obtain a first mixture. The first mixture is cooled to a temperature in the range of 10 °C to 25 °C to initiate crystallization followed by equilibrating under stirring for a time period in the range of 3 hours to 8 hours at a temperature in the range of 10 °C to 25 °C to complete crystallization to obtain a second mixture containing enantiomeric crystals of Indoxacarb comprising R-isomer and S-isomer of Indoxacarb.

The cooling of the filtrate is done by using external source of cooling. The step of cooling the filtrate initiates crystallization of the enantiomeric mixture of Indoxacarb. Further, equilibration is the process of allowing a solution to attain equilibrium for obtaining a specific enantiomeric ratio. The equilibration step is very important for allowing complete crystallization of the enantiomeric mixture, while the impurities stay in the filtrate.

Typically, the cooling of the filtrate and the equilibration of the second mixture is done at a temperature in the range of 15 °C to 20 °C.

In an embodiment, the filtrate is cooled to 17 °C and the equilibration of the second mixture is done at 17 °C.

Typically, the equilibration is done for a time period in the range of 5 hours to 8 hours. In an embodiment, the equilibration is done for 6 hours.

In the next step, the mixture is filtered to isolate the enantiomeric crystals of Indoxacarb. The crystals are washed and dried to obtain an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%. The enantiomeric mixture of Indoxacarb comprises crystals of R-isomer and S-isomer, wherein the S-isomer crystals are present in an amount in the range of 75% to 90% of the enantiomeric mixture.

The step of washing the crystals is done using a fluid medium selected from the group consisting of methanol, ethanol, 2-propanol, 1-butanol and cyclohexanol. The washing of the crystals with the fluid medium ensures complete removal of the impurities in the filtrate, thereby leading to higher purity. In an embodiment, the crystals are washed using 2-propanol.

The step of drying the mass is done under vacuum at a temperature in the range of 35 °C to 45 °C. The temperature range of drying ensures the removal of the fluid medium from the crystals. In an embodiment, the drying is done at 40 °C.

In one embodiment, the enantiomeric mixture of Indoxacarb crystals obtained by the process of the present disclosure has a purity of 98% and the S-isomer crystals are present in an amount of 75% of the enantiomeric mixture. In another embodiment, the enantiomeric mixture of Indoxacarb crystals obtained by the process of the present disclosure has a purity of 99% and the S-isomer crystals are present in an amount of 86% of the enantiomeric mixture.

In an exemplary embodiment, crude Indoxacarb is mixed with 2-propanol to obtain a slurry, wherein the crude Indoxacarb comprises impurities in an amount of 13 wt.%. The slurry is heated to 75 °C to obtain a heated slurry. The heated slurry is cooled to 65 °C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. At least one portion of the warm slurry is filtered at 65 °C, to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The filtrate is mixed with the remaining portion of the warm slurry to obtain a first mixture. The first mixture is cooled to 17 °C to initiate crystallization followed by equilibration under stirring for 6 hours at 17 °C to allow complete crystallization to obtain a second mixture containing enantiomeric crystals of Indoxacarb comprising R-isomer and S-isomer of Indoxacarb. The second mixture is filtered to isolate the enantiomeric crystals of Indoxacarb. The crystals are washed with 2-propanol and dried at

40 °C under vacuum, to obtain an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%.

In another aspect, the present disclosure provides an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%, wherein the enantiomeric mixture of Indoxacarb crystals comprises crystals of R-isomer and S-isomer of Indoxacarb. The S-isomer crystals are present in the range of 75 % to 90% of the enantiomeric mixture.

In one embodiment, the enantiomeric mixture of Indoxacarb crystals has a purity of 99% and the S-isomer crystals are present in an amount of 80% of the enantiomeric mixture. In another embodiment, the enantiomeric mixture of Indoxacarb crystals obtained by the process of the present disclosure has a purity of 99% and the S-isomer crystals are present in an amount of 86% of the enantiomeric mixture.

The commercial sample of Indoxacarb comprises 1:3 ratio of R:S isomers. The conventional process of enhancing the purity leads to reduction in the amount of the active S-isomer. The process of the present disclosure leads to the enhancement in the purity of Indoxacarb while increasing or maintaining the amount of the active S-isomer, thereby avoiding any deterioration in the amount of the active isomer.

The foregoing description of the embodiments has been provided for purposes of illustration and not intended to limit the scope of the present disclosure. Individual components of a particular embodiment are generally not limited to that particular embodiment, but, are interchangeable. Such variations are not to be regarded as a departure from the present disclosure, and all such modifications are considered to be within the scope of the present disclosure.

The present disclosure is further described in light of the following laboratory scale experiments which are set forth for illustration purpose only and not to be construed for limiting the scope of the disclosure. These laboratory scale experiments can be scaled up to industrial/commercial scale and the results obtained can be extrapolated to industrial/commercial scale.

Experimental Details

Experiment 1: Isolation of racemic and enantiomeric Indoxacarb crystals

Example a: Isolation of racemic Indoxacarb (Sample 1A) and enantiomeric crystals of Indoxacarb (Sample 2A)

Crude Indoxacarb (100 g) having purity of 86% (impurities of 14 wt.%) and R: S isomer ratio= 25:75, was placed in a vessel equipped with stirrer and mixed with Isopropyl alcohol (125 ml) to obtain a slurry. The slurry was heated to 75 °C to obtain a heated slurry, which was then cooled to 70°C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. 10 vol.% of the warm slurry was then filtered at 70°C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The racemic Indoxacarb crystals were dried (11 gm) and used for further analysis (Sample 1A). The filtrate was mixed with the remaining slurry and cooled to 18 °C to initiate crystallization followed by equilibrating under stirring for 4 hours to allow complete crystallization to obtain a mixture containing enantiomeric crystals of Indoxacarb comprising R-isomer and S-isomer of Indoxacarb. The mixture was filtered at 18 °C to isolate the enantiomeric crystals of Indoxacarb. The crystals were washed with isopropyl alcohol and then dried under vacuum at 40 °C to get an enantiomeric mixture of Indoxacarb crystals (Sample 2A) (75g) with purity of 98% and enantiomeric ratio of R:S isomer crystals as 25:75.

Example b: Isolation of racemic Indoxacarb (Sample 1B) and enantiomeric crystals of Indoxacarb (Sample 2B)

Crude Indoxacarb (100 g) having purity of 86% and R: S isomer ratio= 30:70, was placed in a vessel equipped with stirrer and mixed with Isopropyl alcohol (100 ml) to obtain a slurry. The slurry was heated to 75 °C to obtain a heated slurry, which was cooled to 60°C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. 15 vol.% of the warm slurry was then filtered at 60°C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The racemic Indoxacarb crystals were dried (15 gm) and used for further analysis (Sample 1B). The filtrate was mixed with the remaining slurry and cooled to 15 °C to initiate crystallization followed by equilibrating under stirring for 6 hours to allow complete crystallization to obtain a mixture containing enantiomeric crystals comprising R-isomer and S-isomer of Indoxacarb. The mixture was filtered at 18 °C to isolate the enantiomeric crystals of Indoxacarb. The crystals were washed with 25 ml isopropyl alcohol and then dried under vacuum at 40 °C to get an enantiomeric mixture of Indoxacarb crystals (71g, Sample 2B) with purity of 98% and enantiomeric ratio of R:S isomer crystals as 25:75.

Example c: Isolation of racemic Indoxacarb (Sample 1C) and enantiomeric crystals of Indoxacarb (Sample 2C)

Crude Indoxacarb (100 g) having purity of 88% and R: S isomer ratio= 25:75, was placed in a vessel equipped with stirrer and mixed with Isopropyl alcohol (100 ml) to obtain a slurry. The slurry was heated to 75 °C to obtain a heated slurry, which was cooled to 70°C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. 15 vol.% of the warm slurry was then filtered at 70°C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The racemic Indoxacarb crystals were dried (14 gm) and used for further analysis (Sample 1C). The filtrate was mixed with the remaining slurry and cooled to 16 °C to initiate crystallization followed by equilibrating under stirring for 6 hours to allow complete crystallization to obtain a mixture containing enantiomeric crystals comprising R-isomer and S-isomer of Indoxacarb. The mixture was filtered at 16 °C to separate the enantiomeric crystals of Indoxacarb. The crystals were washed with 25 ml isopropyl alcohol and then dried under vacuum at 42 °C to get an enantiomeric mixture of Indoxacarb crystals (73g, Sample 2C) with purity of 99% and enantiomeric ratio of R:S isomer crystals as 20:80.

Example d: Isolation of racemic Indoxacarb (Sample 1D) and enantiomeric crystals of Indoxacarb (Sample 2D)

Crude Indoxacarb (100 g) having purity of 87% and R: S isomer ratio= 24:76, was placed in a vessel equipped with stirrer and mixed with Isopropyl alcohol (100 ml) to obtain a slurry. The slurry was heated to 75 °C to obtain a heated slurry, which was cooled to 70°C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb. 20 vol.% of warm slurry was then filtered at 65°C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate. The racemic Indoxacarb crystals were dried (15 gm) and used for further analysis (Sample 1D). The filtrate was mixed with the remaining slurry and cooled to 17°C to initiate crystallization followed by equilibrating under stirring for 6 hours to allow complete crystallization to obtain a mixture containing enantiomeric crystals comprising R-isomer and S-isomer of Indoxacarb. The mixture was filtered at 17°C to separate the enantiomeric crystals of Indoxacarb. The crystals were washed with 40 ml isopropyl alcohol and then dried under vacuum at 40 °C to obtain an enantiomeric mixture of crystals of Indoxacarb (72g Sample 2D) with purity of 99% and enantiomeric ratio of R:S isomer crystals as 14:86.

Experiment 2: Differential scanning calorimetry (DSC) analysis:

The racemic Indoxacarb crystals (sample 1A) and enantiomeric Indoxacarb crystals (sample 2A), as obtained from Example (a) were subjected to Differential scanning calorimetry (DSC) analysis as shown in Figures 1 and 2 respectively. The DSC analysis of sample 1A shows a single peak in the range of 144.5 °C to 150.7 °C, corresponding to the melting temperature of racemic Indoxacarb, whereas the DSC analysis of sample 2A shows two peaks, wherein a peak in the range of 87.5 °C to 93.6 °C corresponds to the enantiomeric Indoxacarb (S-isomer or R-isomer) and a peak in the range of 143.1 °C to 147.3 °C, corresponds to the racemic Indoxacarb.

Experiment 3: X-Ray Diffraction (XRD) data:

The samples 1A and 2A, as obtained from Example (a) were subjected to X-Ray Diffraction (XRD) analysis as shown in Figures 3 and 4 respectively.

As observed in Figure 4, the sample 2A shows most of the significant expected peaks, thus confirming the presence of the crystalline form of Indoxacarb.

The process of the present disclosure is simple and effective wherein the enhancement in purity does not decrease the amount of S-isomer. The Indoxacarb crystals obtained by the process of the present disclosure have higher purity and either same or higher amount of the S-isomer than the crude Indoxacarb.

TECHNICAL ADVANCEMENTS

The present disclosure described herein above has several technical advantages including but not limited to the realization of a process for preparing an enantiomeric mixture of Indoxacarb crystals that:

- provides specific purity without deterioration in the amount of the active S-isomer; and
- is simple and economical.

Throughout this specification the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated element, integer or step,

or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The use of the expression "at least" or "at least one" suggests the use of one or more elements or ingredients or quantities, as the use may be in the embodiment of the disclosure to achieve one or more of the desired objects or results.

Any discussion of documents, acts, materials, devices, articles or the like that has been included in this specification is solely for the purpose of providing a context for the disclosure. It is not to be taken as an admission that any or all of these matters form a part of the prior art base or were common general knowledge in the field relevant to the disclosure as it existed anywhere before the priority date of this application.

The numerical values mentioned for the various physical parameters, dimensions or quantities are only approximations and it is envisaged that the values higher/lower than the numerical values assigned to the parameters, dimensions or quantities fall within the scope of the disclosure, unless there is a statement in the specification specific to the contrary.

While considerable emphasis has been placed herein on the components and component parts of the preferred embodiments, it will be appreciated that many embodiments can be made and that many changes can be made in the preferred embodiments without departing from the principles of the disclosure. These and other changes in the preferred embodiment as well as other embodiments of the disclosure will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the disclosure and not as a limitation

CLAIMS:

1. A process for obtaining an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%, said process comprising the following steps:
   a) mixing crude Indoxacarb with a solvent to obtain a slurry, wherein the crude Indoxacarb comprises impurities in an amount in the range of 10 wt.% to 15 wt.%;
   b) heating said slurry to a temperature in the range of 74 °C to 85 °C to obtain a heated slurry;
   c) cooling said heated slurry to a temperature in the range of 55 °C to 70 °C to allow partial crystallization and obtain a warm slurry comprising crystals of racemic Indoxacarb;
   d) filtering at least one portion of said warm slurry at a temperature in the range of 55 °C to 70 °C to isolate a mass comprising the crystals of racemic Indoxacarb and obtain a filtrate;
   e) mixing said filtrate with the remaining portion of said warm slurry to obtain a first mixture;
   f) cooling said first mixture to a temperature in the range of 10 °C to 25 °C to initiate crystallization followed by equilibrating under stirring for a time period in the range of 3 hours to 8 hours to allow complete crystallization to obtain a second mixture containing enantiomeric crystals comprising R-isomer and S-isomer of Indoxacarb;
   g) filtering said second mixture to isolate said enantiomeric crystals of Indoxacarb; and
   h) washing and drying said crystals to obtain an enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%; wherein said enantiomeric mixture of Indoxacarb comprises crystals of R-isomer and S-isomer, wherein the S-isomer crystals are present in an amount in the range of 75% to 90% of said enantiomeric mixture.

2. The process as claimed in claim 1, wherein the crude Indoxacarb comprises an enantiomeric mixture containing crystals of R-isomer and S-isomer, wherein the crystals of S-isomer in the crude Indoxacarb are present in an amount of at least 70 % of said enantiomeric mixture.

3. The process as claimed in claim 1, wherein the weight-volume ratio of the crude Indoxacarb and the solvent in step (a) is in the range of 1:0.8 to 1:1.5.

4. The process as claimed in claim 1, wherein said solvent is selected from the group consisting of aliphatic alcohols with C_1 to C_{10} carbon atoms and cyclic alcohols.

5. The process as claimed in claim 1, wherein said solvent is selected from the group consisting of methanol, ethanol, 2-propanol, 1-butanol and cyclohexanol, and wherein

the washing in step (h) is done by using a fluid medium selected from the group consisting of methanol, ethanol, 2-propanol, 1-butanol and cyclohexanol.

6. The process as claimed in claim 1, wherein said at least one portion of said warm slurry in step (d) is in the range of 10 vol.% to 20 vol.%.

7. The process as claimed in claim 1, wherein drying in step (h) is done under vacuum at a temperature in the range of 35 °C to 45 °C.

8. The process as claimed in claim 1, wherein said process comprises the following steps:
   a) mixing crude Indoxacarb with a solvent to obtain a slurry, wherein the crude Indoxacarb comprises impurities in an amount of 13 wt.%, and wherein the crude Indoxacarb comprises an enantiomeric mixture containing crystals of R-isomer and S-isomer, wherein the S-isomer crystals in the crude Indoxacarb are present in an amount of 70% of said enantiomeric mixture;
   b) heating said slurry to 75 °C to obtain a heated slurry;
   c) cooling said heated slurry to 65 °C to allow partial crystallization and obtain a warm slurry comprising crystals of the racemic Indoxacarb;
   d) filtering at least one portion of said warm slurry at said temperature in step (c) to isolate a mass comprising the crystals of the racemic Indoxacarb and obtain a filtrate;
   e) mixing said filtrate with the remaining portion of said warm slurry to obtain a first mixture;
   f) cooling said first mixture to 17 °C to initiate crystallization followed by equilibrating under stirring for 6 hours at 17 °C to allow complete crystallization to obtain a second mixture containing enantiomeric crystals comprising R-isomer and S-isomer of Indoxacarb;
   g) filtering said second mixture to isolate said enantiomeric crystals of Indoxacarb; and
   h) washing and drying said crystals to obtain an enantiomeric mixture of Indoxacarb crystals having purity of 99%; wherein said enantiomeric mixture comprises crystals of R-isomer and S-isomer, wherein the S-isomer crystals are present in an amount of 86% of said enantiomeric mixture.

9. An enantiomeric mixture of Indoxacarb crystals having purity in the range of 95% to 99.5%, wherein said enantiomeric mixture comprises crystals of R-isomer and S-isomer of Indoxacarb, and wherein the S-isomer crystals are present in an amount in the range of 75 % to 90% of the enantiomeric mixture.

10. The enantiomeric mixture of Indoxacarb crystals as claimed in claim 9, wherein said Indoxacarb crystals have purity of 99%, and wherein the S-isomer crystals are present in an amount of 86% of the enantiomeric mixture.

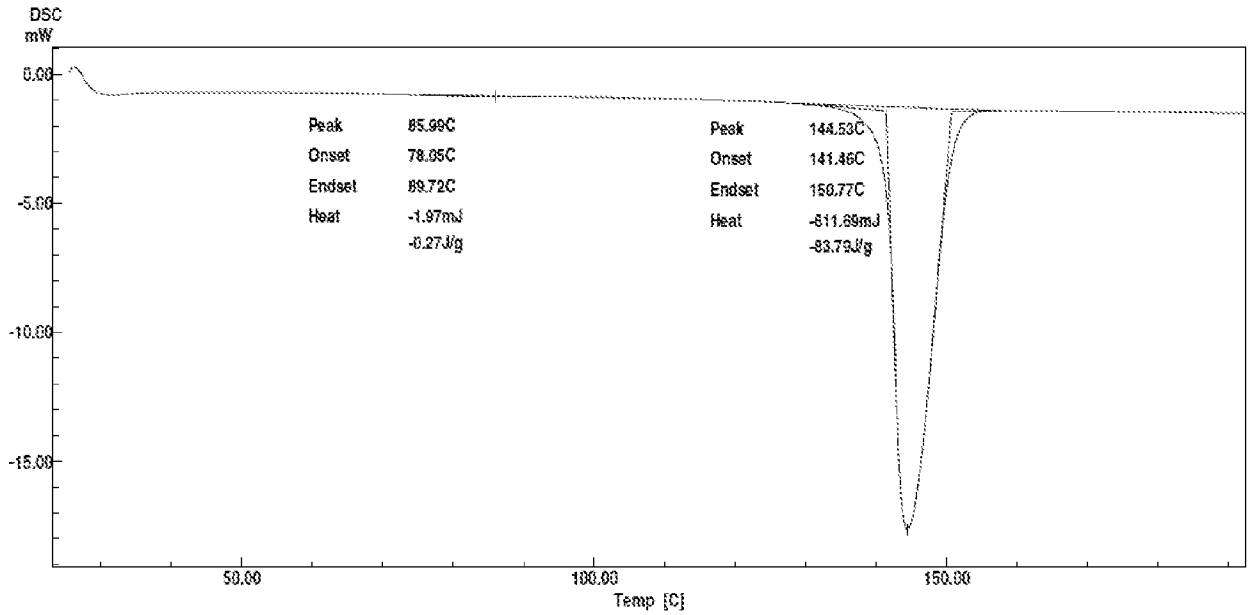

DSC
mW
0.00
-5.00
-10.00
-15.00
Peak 85.99C
Onset 78.85C
Endset 89.72C
Heat -1.97mJ
-0.27J/g
Peak 144.53C
Onset 141.46C
Endset 150.77C
Heat -611.69mJ
-83.79J/g
50.00
100.00
150.00
Temp [C]

Figure 1

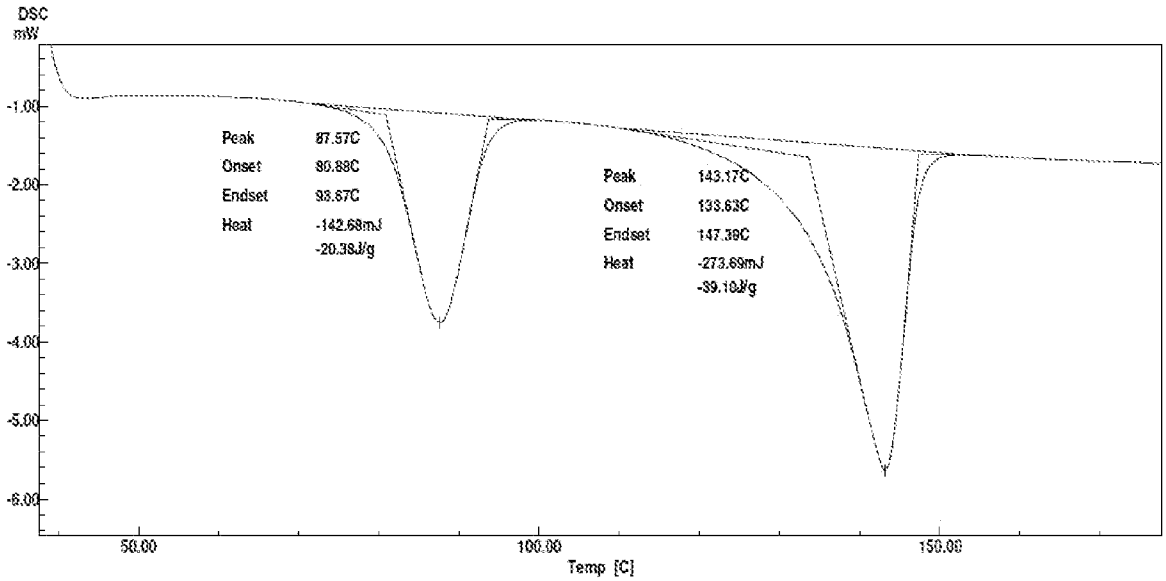

DSC
mW
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
Peak 87.57C
Onset 80.88C
Endset 93.67C
Heat -142.68mJ
-20.38J/g
Peak 143.17C
Onset 133.63C
Endset 147.39C
Heat -273.69mJ
-39.10J/g
50.00
100.00
150.00
Temp [C]

Figure 2

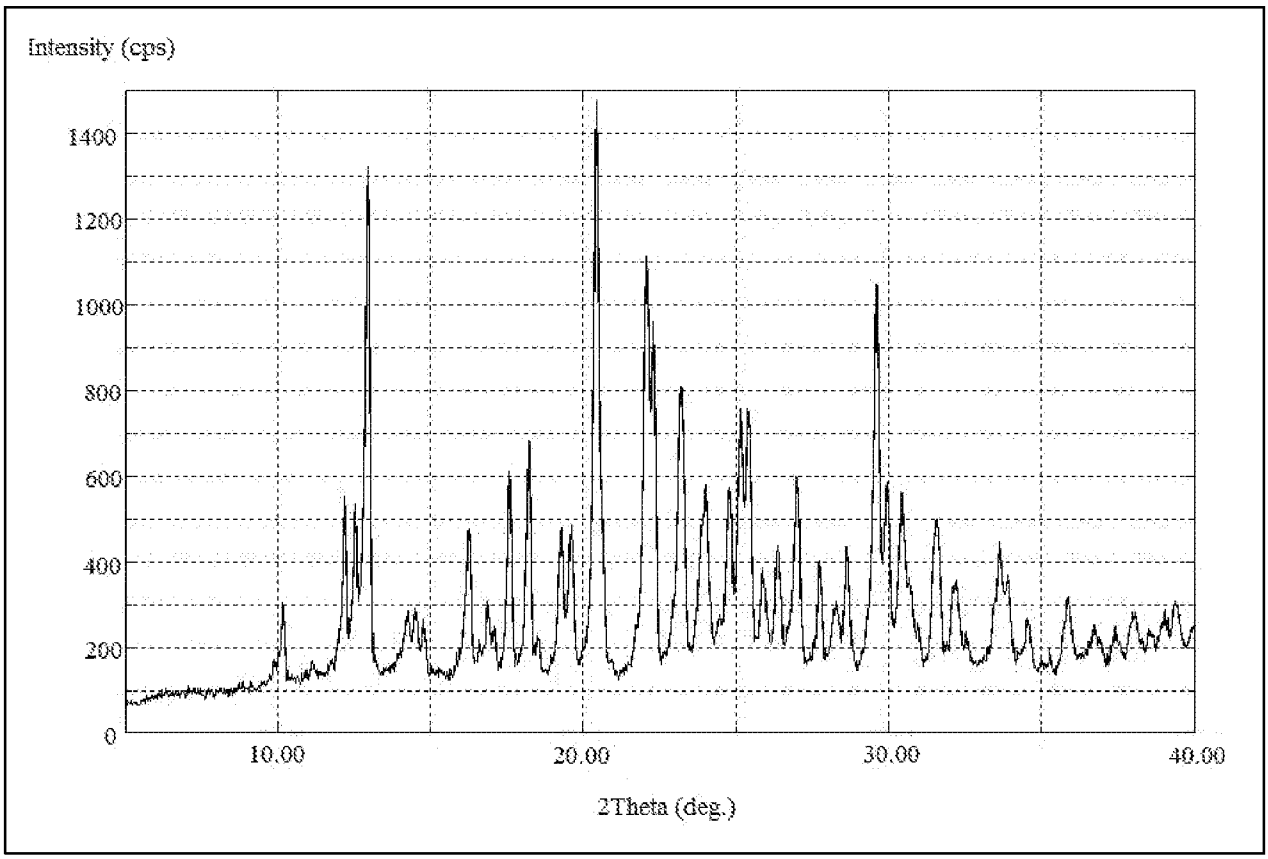

Intensity (cps)
1400
1200
1000
800
600
400
200
0
10.00
20.00
30.00
40.00
2Theta (deg.)

Figure 3

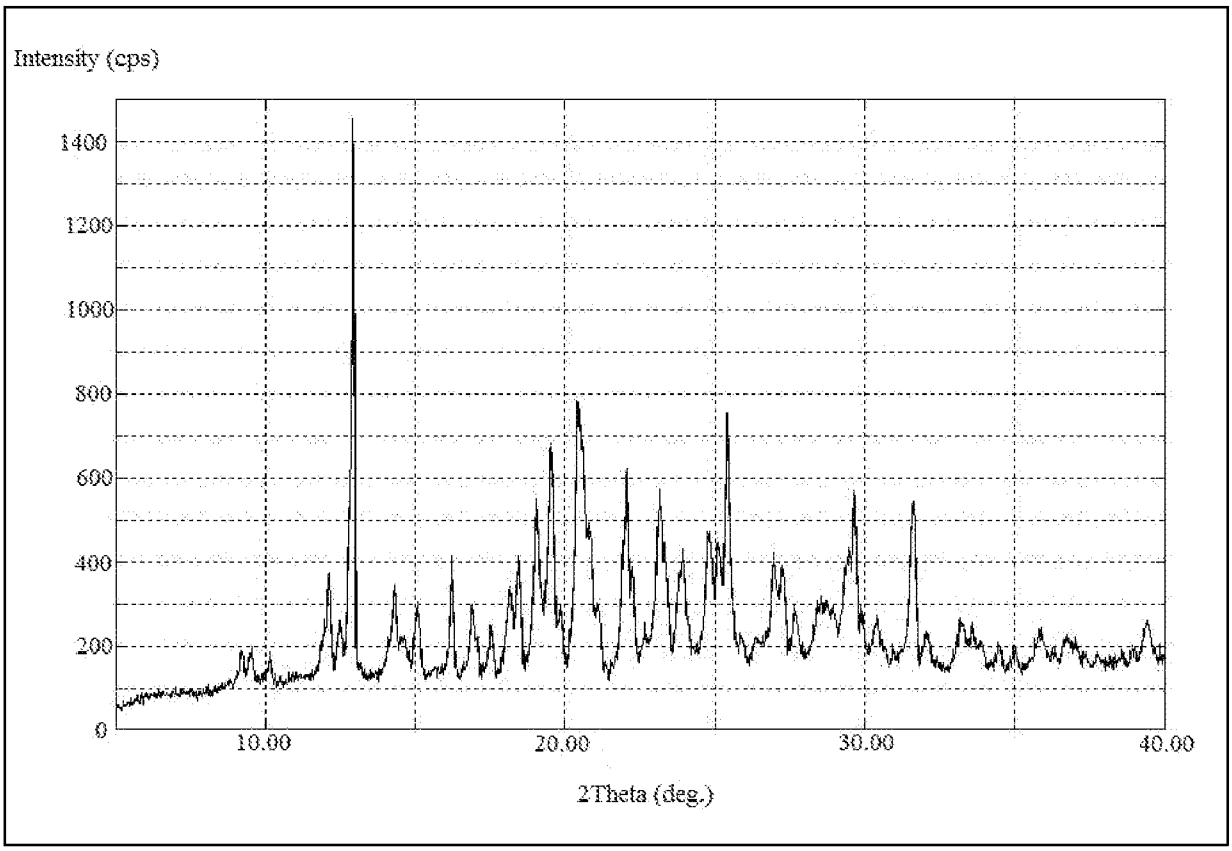

Intensity (cps)
1400
1200
1000
800
600
400
200
0
10.00
20.00
30.00
40.00
2Theta (deg.)

Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/056457

A. CLASSIFICATION OF SUBJECT MATTER
C07D273/04 Version=2020.01

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)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN104311502 A (NANTONG SHI ZHUANG CHEMICAL CO LTD) 28 January 2015 (28-01-2015) Embodiments 1-5	1-8
X	IN530MUM2005 A (GHARDA CHEMICALS LTD [IN]) 24 February 2006 (24-02-2006) examples 1-2	9-10

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12-10-2020	12-10-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Parameswar Sau Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2020/056457

Citation	Pub.Date	Family	Pub.Date
IN 530MUM2005 A	24-02-2006	TW 200716510 A	01-05-2007
		AR 053864 A1	23-05-2007
		MY 141190 A	31-03-2010