

Crystallization and Polymorphism-Scalable Process for Celecoxib and It's Polymorph Form-3 (Non- Steroidal Anti-Inflammatory Drug (NSAID))

Krishnasarma Pathy* and MS Chakravarthy

Research Centre Lucknow, India

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*Corresponding author: Krishna Sarma Pathy, Head -QC, QA/R&D-IPL Research Centre Lucknow, India

Abstract

The present process provides an improved process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (Celecoxib) and its purification and crystallization to produce polymorph. The present process, which describes the manufacturing process of Celecoxib, which is a non-steroidal anti-inflammatory drug (NSAID), has the advantage of scaling up to the industrial level of production. The process uses safe reagents in the process which makes it for industrial scale operations. The yields in the process are high, which makes it a cost-effective process. Formation of isomers are less compared with the all existing process, which makes it effective to make it to the pharmacopoeia grade. Residual solvents play a very important role in the impurity profile of APIs as per the ICH Guidelines ICH Q3C (R4). In this process by carrying out the final step of condensation in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of.

Keywords: Non-steroidal anti-inflammatory drug (NSAID); Celecoxib; Cyclooxygenase 2; X-ray diffraction; Polymorphism; Process

Discussion

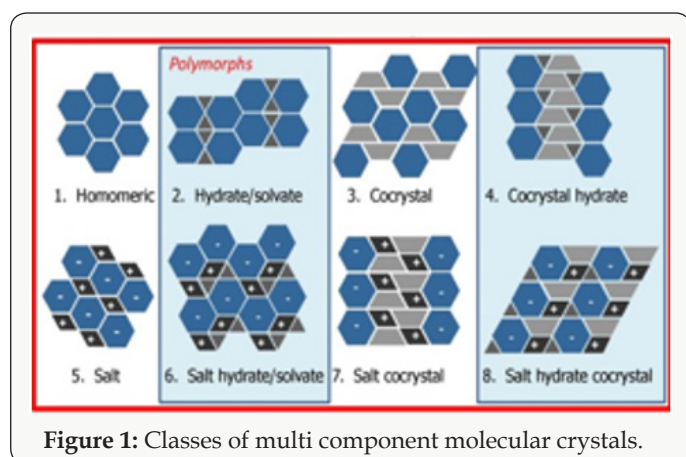


Figure 1 present process relates to “AN IMPROVED PROCESS FOR THE PREPARATION OF CELECOXIB POLYMORPH FORM”. Celecoxib is designated chemically as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)- 1H-pyrazol-1-yl] benzene sulphonamide and is a diaryl-substituted pyrazole [1]. The compound has the following structure (Figure 2).

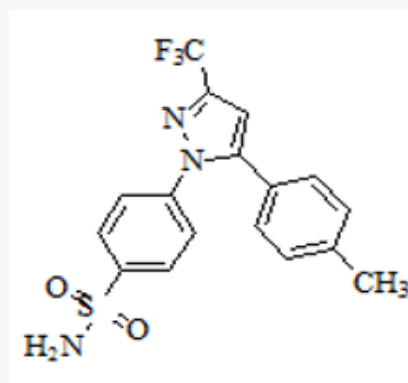


Figure 2: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide.

The drug is currently marketed as Celebrex® in the United States of America by Pharmacia Corporation. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) [1] mainly used in treatment of arthritis, pain, menstrual cramps, and colonic polyps. Celecoxib blocks the enzyme (cyclooxygenase 2) which

makes prostaglandins, resulting in lowering the concentrations of prostaglandins. As a consequence, reduction in inflammation and its accompanying pain, fever, swelling and tenderness. The manufacture of Celecoxib has been described in various patents and to cite a few references, G. D. Searl & Co. has disclosed method for preparation of Celecoxib [2-3] in US 5,466,823 which is as under: US 5,134,142 [2], US 5,563,165, US 6,150,534, US 5,892,053,

US 2007/0004924, US 2008/0234491, EP 1,528,058, EP 1,167,355, EP 2,246,332, WO 01/42221, WO 03/090730, WO05/014546, WO 06/051340, WO 08/145733, and WO 2010/095024 have also described the synthesis of Celecoxib Reddy et al in their publication in Org. Process Res. Dev., 2009, 13(1), pp 98-101. have disclosed the synthesis (Figure 3).

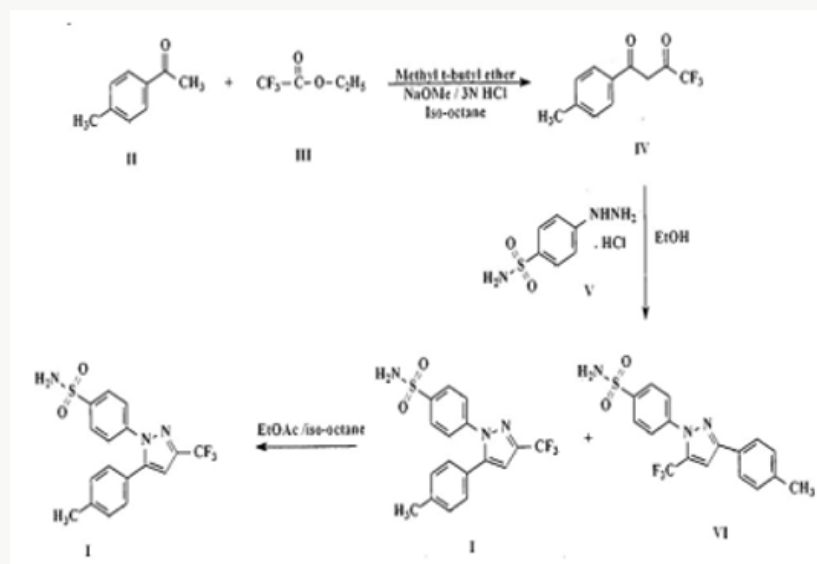


Figure 3: Manufacture of Celecoxib.

Detailed Description of the Drawings

Figure 1 describes the powder X-ray diffraction pattern of the Celecoxib Polymorph; Figure 2 illustrates 2θ values. Figure 3 depicts the DSC thermogram taken at 10°C/min over a temperature range of 30°C to 200°C for Celecoxib polymorphic form.

Description of the Process

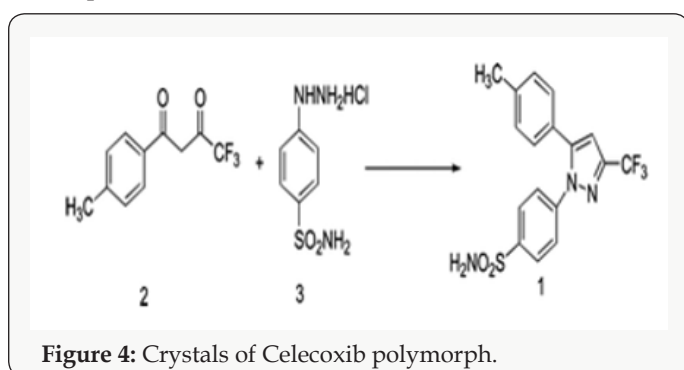


Figure 4: Crystals of Celecoxib polymorph.

The present procedure describes the preparation of Celecoxib by a novel process and its crystallization to polymorphic form. The present process for the preparation of Celecoxib by a process involving condensation of 4,4,4-trifluoro-1-[4-(methyl) phenyl]-butane-1,3-dione [1] with sulphonamido phenyl hydrazine hydrochloride [2] in an aqueous medium to give Celecoxib [3]. This is followed by crystallization from a mixture of solvents [4-8] containing Aromatic hydrocarbon and aliphatic ketone. In

the condensation reaction the reactants are added in water and reactions done at ambient temperature. The crude Celecoxib is isolated by filtration. In the for purification of Celecoxib and its crystallization to polymorphic FORM Preparing a solution of Crude Celecoxib in a solvent mixture comprising of an aliphatic ketone (Acetone) and an aromatic hydrocarbon (Toluene) at reflux temperature followed by cooling crystallization to give crystals of Celecoxib polymorph [8-12] (Figure 4).

Table 1:

| Signal | Assignment/Remarks |
|---------------------|-------------------------------------|
| 2.3 ppm | 3 H, methyl, Singlet |
| 3.337 and 3.329 ppm | Residual H of DMSO d6, ignore |
| 7.20 ppm | 4 H, Aromatics, multiplet |
| 7.53 ppm | 3 H, Aromatics, 1 H, H-4 (pyrazole) |
| 8.8 ppm | 1 H, Aromatic, doublet |

In this process by carrying out the final step of condensation in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of. The yields in the process are higher compared to the prior art, which makes it a cost-effective process. Formation of isomers are less compared with the prior art, which makes it effective to make it to the pharmacopoeia grade. Residual solvents play a very important role in the impurity profile of APIs as per the ICH Guidelines ICH Q3C (R4). In this process

by carrying out the final step of condensation in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of [13,14]. The crystallization conditions are well established to give crystalline polymorph. The powder X-Ray diffraction pattern of the Celecoxib is given in Figure 1 and 2θ

values are given in Table 1 of Figure 2. The differential scanning calorimeter graph of the Celecoxib polymorph under specific conditions shows the melting point around 162.7°C. The DSC of Celecoxib is given in Figures 3,5, and 6.

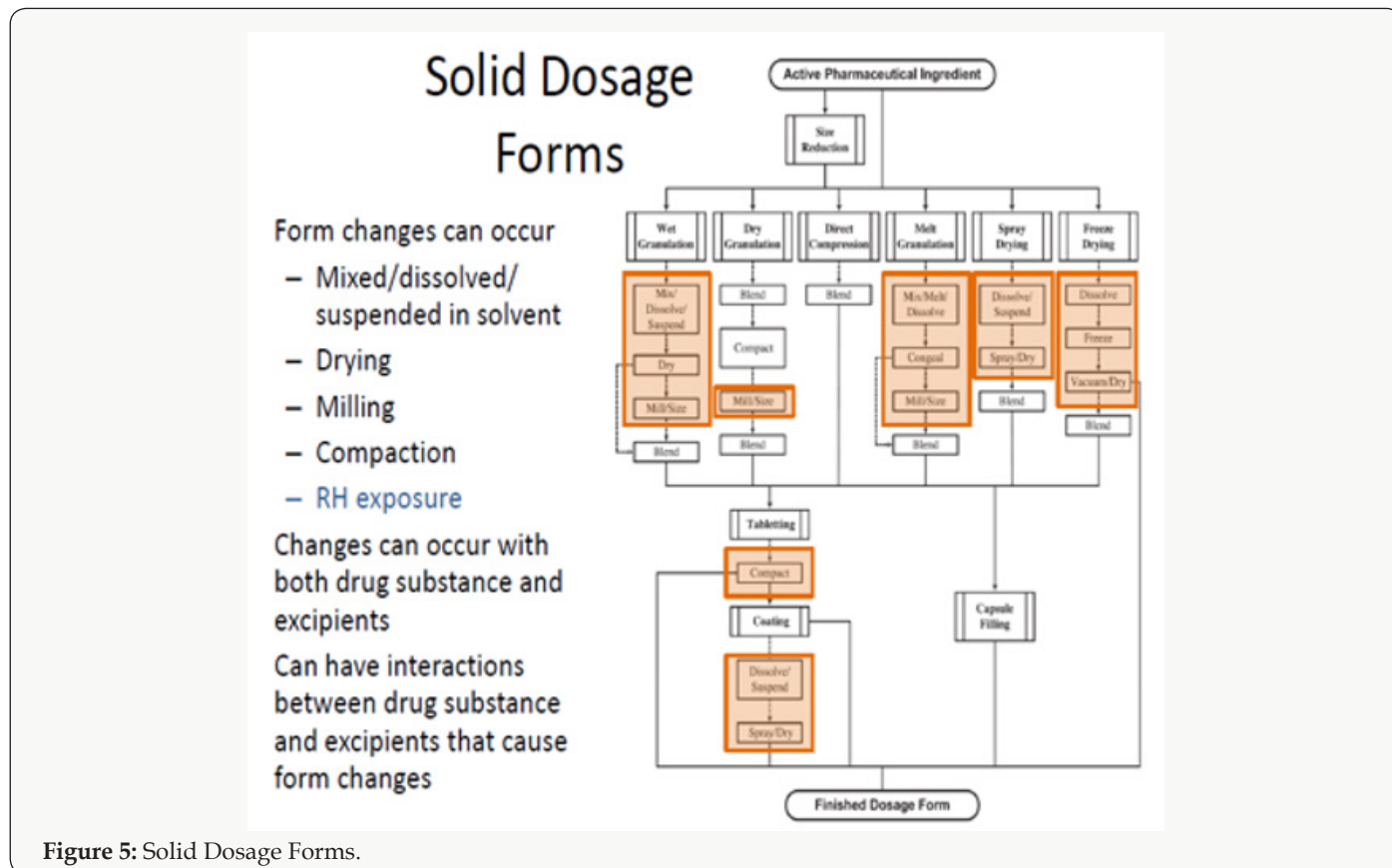


Figure 5: Solid Dosage Forms.

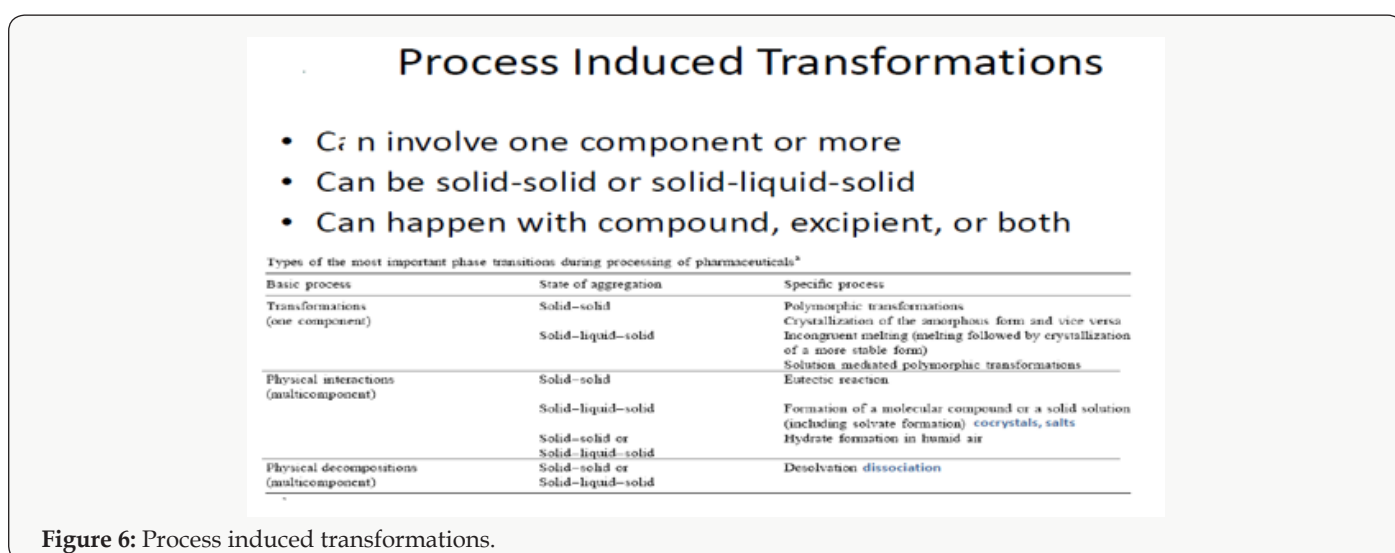


Figure 6: Process induced transformations.

Solid Forms

- Propensity to produce different forms not significantly different for salts and non-salts.
- Need more data on co-crystals (Figure 7).

The details of the new methods for preparation of celecoxib are further illustrated in the following examples.

Example 1: Preparation of Celecoxib

In a 20 liter 3-necked flask, equipped with stirrer, thermometer

and reflux condenser, deionized water (7.9 Liter) is charged and mixture of 4,4,4-trifluoro-1-[4-(methyl) phenyl]-butane-1,3-dione (1.6Kg; 6.95×10^3 mmoles) and 4-sulphonamido phenyl hydrazine hydrochloride (1.7Kg; 7.57×10^3 mmoles), a resultant mixture was

heated at 75°C to 80°C and maintained for 5 hours. The reaction mixture was cooled to 25°C to 30°C to give a slurry. The slurry was filtered and washed with water (3.2liter) wet- cake was collected and further processed for purification as given below.

Table 2. Percentages of Forms from Polymorph Screening

| | all compounds [count (%)] | salts [count (%)] | non-salts [count (%)] |
|-----------------------------------------|---------------------------------|----------------------|--------------------------|
| multiple forms ^a | 220 (89) | 86 (91) | 116 (91) |
| multiple crystalline forms ^b | 200 (82) | 77 (81) | 105 (82) |
| polymorphs ^c | 118 (48) | 37 (39) | 71 (55) |
| hydrates | 94 (38) | 46 (48) | 38 (30) |
| solvates | 78 (32) | 34 (36) | 36 (28) |
| noncrystalline | 118 (48) | 51 (54) | 55 (43) |
| total compounds | 245 | 95 | 128 |

^a Crystalline polymorphs, hydrates, and solvates plus noncrystalline forms. ^b Crystalline polymorphs, hydrates, and solvates. ^c Crystalline polymorphs.

Figure 7: Percentages of forms from Polymorph Screening.

a) Purification and Crystallization to Give Polymorph:

Celecoxib wet-cake obtained in the process described above was taken into 20 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, mixture of acetone (0.54liter) and toluene (10.8liter) was added and the reaction mixture was heated to 80°C to 85°C for 30 minutes. Activated carbon (0.3Kg) was added and the reaction mixture was further heated to 80°C to 85°C. The reaction mixture was cooled to 25°C -30°C. The slurry was filtered, washed with toluene and then dried at 70°C to yield the Celecoxib polymorph compound 1.35 kg (HPLC purity-99.8% & molar yield; 50.9%).

IR: 3340, 3240, 1600, 1500, 1350, 1280, 1235, 1160, 980, 910, 840, 800, 760, 635, 560, 530 cm^{-1} (KBr pellet)

Proton NMR: Solvent: DMSO d₆, 300 MHz.

Example 2: Preparation of Celecoxib

In a 20liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, charge deionized water(9Liter) and mixture of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione(1.6Kg; 6.95×10^3 mmoles) and 4-sulphonamido phenyl hydrazine hydrochloride(1.7Kg; 7.57×10^3 mmoles), a resultant mixture was heated at 90°C to 100°C and maintained for 5 hours. The reaction mixture was cooled to 25°C to 30°C. The slurry was filtered and washed with water (3.2liter) wet-cake was collected and further processed for purification as given below.

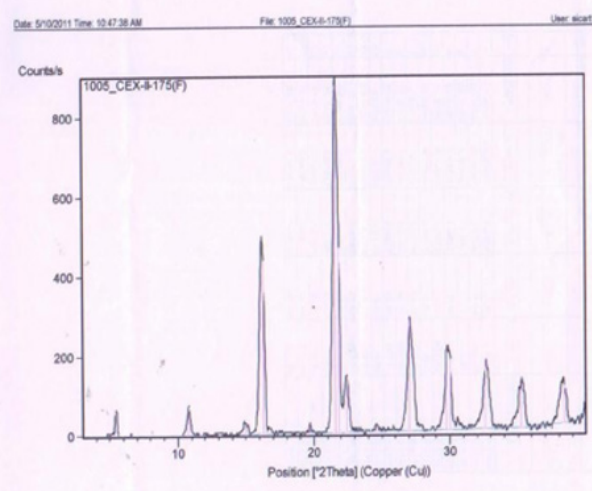


Figure 8: Powder X-Ray diffraction pattern of the Celecoxib.

a) Purification and crystallization to give Polymorph: Celecoxib wet-cake obtained in the process described above was taken into 20liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser; mixture of acetone (0.54liter) and toluene (10.8liter) was added and the reaction mixture was heated to 80°C to 85°C for 30 minutes. Activated carbon (0.3Kg) was

added and the reaction mixture was further heated to 80°C to 85°C. The reaction mixture was cooled to 25°C -30°C. The separated solid was filtered, washed with toluene and then dried at 70°C to yield the Celecoxib polymorph compound 1.24 kg (HPLC purity-99.3% & molar yield; 47%) (Figures 8-11c).

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|------------------------------------------------------------------------------|--------------|--------------------|--------------------|------------------|--------------|--------------------|
| MOTA BAZAR - VALLABH VIDYANAGAR - 388 120 | | | | | | |
| No. | Visible | Dataset Name | Start pos. [°2Th.] | End pos. [°2Th.] | Step [°2Th.] | Measured Date/Time |
| 1 | TRUE | 1005_CEX-II-175(F) | 3.01 | 39.99 | 0.02 | 5/10/2011 10:28 |
| No. | Pos. [°2Th.] | d-spacing | Significance | Rel. Int. [%] | Height | FWHM [°2Th.] |
| 1 | 5.4088 | 16.33928 | 3.1387 | 9.86 | 64.67 | 0.1968 |
| 2 | 10.8034 | 8.18943 | 1.1256 | 7.64 | 71.62 | 0.1378 |
| 3 | 13.0126 | 6.80362 | 1.891 | 2 | 5.45 | 0.4723 |
| 4 | 15.0126 | 5.90145 | 1.6412 | 7.38 | 24.2 | 0.3936 |
| 5 | 16.2935 | 5.44029 | 9.2472 | 100 | 437.32 | 0.2952 |
| 6 | 19.6896 | 4.50894 | 0.9851 | 2.04 | 22.3 | 0.1181 |
| 7 | 21.603 | 4.1137 | 1.0274 | 80.09 | 875.58 | 0.1181 |
| 8 | 21.8734 | 4.06345 | 0.9792 | 42.77 | 467.65 | 0.1181 |
| 9 | 22.4507 | 3.96026 | 1.4827 | 21.45 | 140.72 | 0.1968 |
| 10 | 23.824 | 3.735 | 0.8233 | 0.45 | 4.88 | 0.1181 |
| 11 | 24.5936 | 3.61984 | 0.833 | 4.77 | 13.03 | 0.4723 |
| 12 | 27.054 | 3.29597 | 0.8743 | 25.62 | 280.08 | 0.1181 |
| 13 | 29.7841 | 2.99977 | 1.0088 | 31.13 | 204.23 | 0.1968 |
| 14 | 30.0469 | 2.97413 | 1.1786 | 19.03 | 178.3 | 0.1378 |
| 15 | 32.6341 | 2.74401 | 1.6601 | 36.52 | 171.12 | 0.2755 |
| 16 | 35.3029 | 2.54245 | 1.6827 | 26.54 | 124.36 | 0.2755 |
| 17 | 38.4104 | 2.34361 | 4.8435 | 40.55 | 95 | 0.551 |

Figure 9: 2θ values.

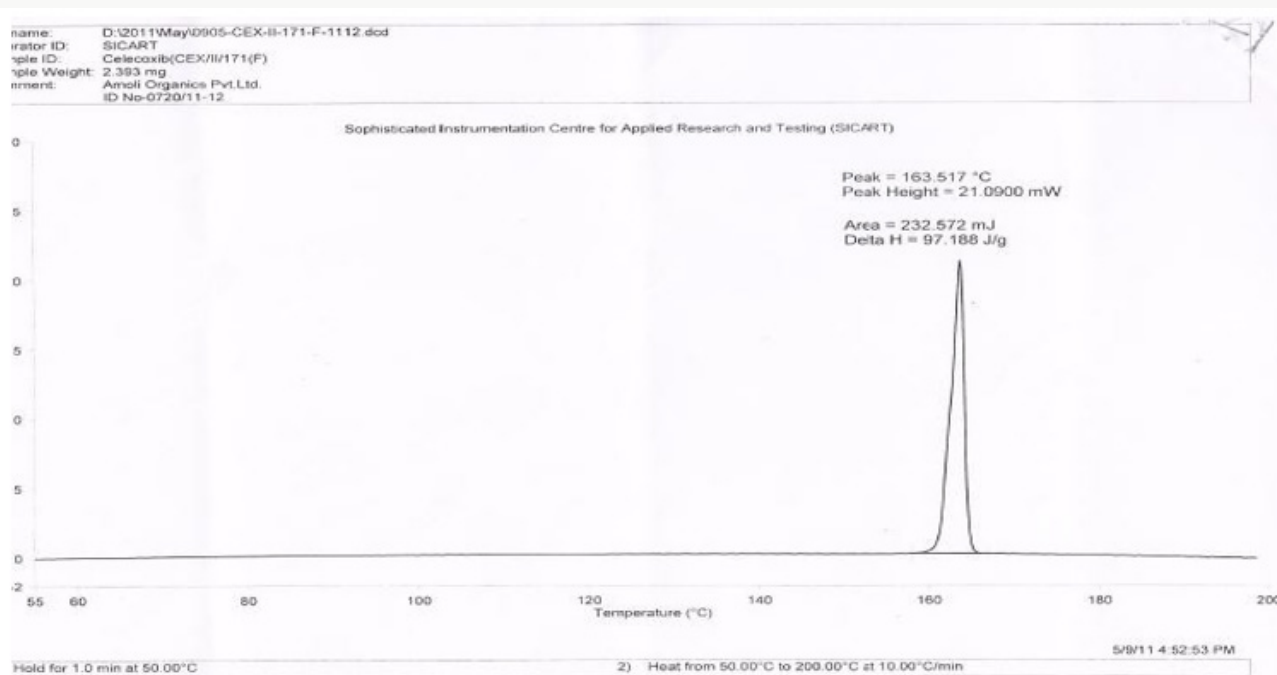
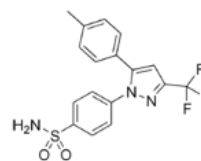


Figure 10: DSC of Celecoxib.

Suspension



- Celecoxib
 - Three unsolvated forms (I, II III)
 - Form III thermodynamically stable form at RT
 - Two solvates: N,N-dimethyl acetamine and N,N-dimethyl formamide (DMF)
- Suspension formulation made with Form III

Representative Formulations of Celecoxib Suspensions

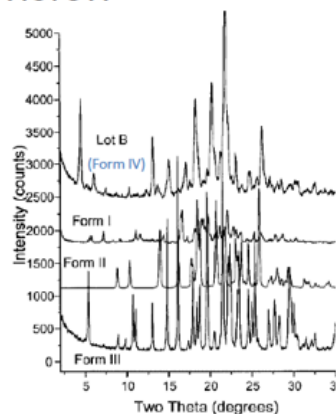
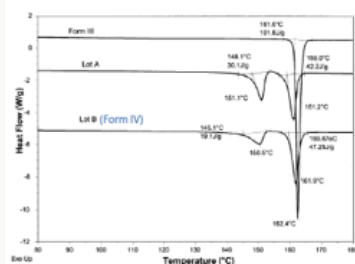
| Ingredient | % w/w | | | | | |
|------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | Lot A | Lot B | Lot C | Lot D | Lot E | Lot F |
| Celecoxib | 1.77 | 1.20 | 1.77 | 1.77 | 1.77 | 1.77 |
| HPMC 2910 USP 15 | 4 | 1 | 5 | 5 | 2.5 | 5 |
| PEG 400 | 4.13 | 2.9 | 4.13 | 4.13 | 4.13 | 4.13 |
| Polysorbate 80 | 1 | 1 | 1 | 1 | 0.5 | 0 |
| PVP K90 | 0 | 1 | 0 | 2 | 1 | 2 |
| Sodium benzoate | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Citric acid | 1.31 | 1.31 | 1.31 | 1.31 | 1.31 | 1.31 |
| Sodium citrate | 1.11 | 1.11 | 1.11 | 1.11 | 1.11 | 1.11 |
| Sucrose | 30 | 30 | 0 | 30 | 15 | 0 |
| Tutti frutti flavoring | 0 | 0 | 0.05 | 0.05 | 0.05 | 0.05 |
| DI water | q.s. to 100 | q.s. to 100 | q.s. to 100 | q.s. to 100 | q.s. to 100 | q.s. to 100 |

Figure 11a

Suspension

XRPD showed Lot B contained a new form of celecoxib (Form IV)
Upon heating, Form IV melts and converts to Form III

IPA slurry with Forms III and IV show Form III is more stable at RT

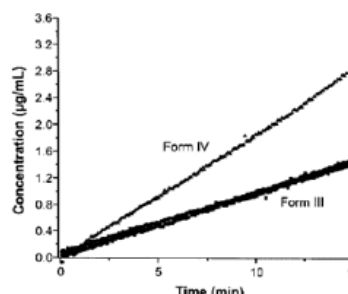


Powder X-ray comparison of the precipitated celecoxib Lot B to the three known crystal forms of celecoxib.

Figure 11b

Suspension

- Metastable Form IV produced from formulation process
- Found concentrations and ratio of HPMC and Polysorbate 80 were critical to the generation of Form IV
- Form IV is 2-3X more soluble than Form III
- Formulations with Form IV are stable at 40 °C for at least 6 months and at 25 °C for at least 16 months
- Possible to stabilize metastable Form IV in suspension and achieve higher bioavailability
- Processing conditions and excipients can affect form; excipients can stabilize forms



Rotating disk dissolution for Form IV and Form III of celecoxib.

Figure 11c

Conclusion

The distinct advantage of the present method of preparation over the prior art can be summarized as per below:

The present process, which describes the manufacturing process of Celecoxib, which is a non-steroidal anti-inflammatory drug (NSAID), has the advantage of scaling up to the industrial level of production. The process uses safe reagents in the process which makes it for industrial scale operations. The present process provides an improved process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (Celecoxib) and its purification and crystallization to produce polymorph. The yields in the process are high compared to existing process which makes it a cost-effective process. Formation of isomers are less compared with the prior art, which makes it effective to make it to the pharmacopoeia grade. In this process by carrying out the final step of condensation in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of. The yields in the process are higher compared to the prior art, which makes it a cost-effective process. Residual solvents play a very important role in the impurity profile of APIs as per the ICH Guidelines ICH Q3C (R4).

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