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(54) Title: SOLID STATE FORMS OF ETORICOXIB SALTS

(57) Abstract: Provided herein are novel solid state forms of etoricoxib salts, process for their preparation, pharmaceutical compositions, and method of treating thereof. The etoricoxib salts include an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt, or a tosylate salt. The solid state forms of etoricoxib salts disclosed herein are useful for preparing etoricoxib free base with high purity.

SOLID STATE FORMS OF ETORICOXIB SALTS

CROSS REFERENCE TO RELATED APPLICATION

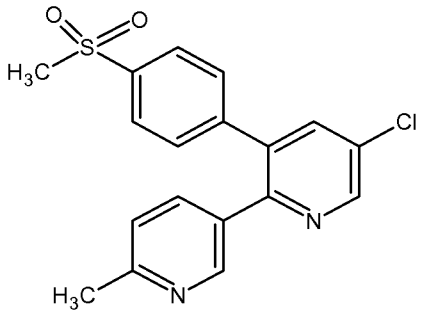
This application claims the benefit of priority to Indian provisional application No. 1898/CHE/2010, filed on July 5, 2010, which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to novel solid state forms of etoricoxib salts, processes for their preparation, pharmaceutical compositions, and methods of treating thereof. The novel solid state forms of etoricoxib salts are useful for preparing etoricoxib free base with high purity. The present disclosure further relates to an improved process for the preparation of highly pure etoricoxib.

BACKGROUND

[0002] U.S. Patent No. 5,861,419 (herein after referred to as the '419 patent) discloses a variety of substituted pyridines, processes for their preparation, pharmaceutical compositions comprising the compounds, and method of use as selective cyclooxygenase-2 (COX-2) inhibitors. A selective COX-2 inhibitor has anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug. Among them, etoricoxib, 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine, is a COX-2 inhibitor and it is indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis. Etoricoxib is represented by the following structural formula:



[0003] Etoricoxib is sold by Merck Sharp & Dohme Limited under the brand name ARCOXIA®. Etoricoxib and its hydrochloride salt are described in the '419 patent. While

the '419 application mentions that some of the disclosed compounds can form salts with pharmaceutically acceptable non-toxic acids, including inorganic and organic acids; no salts of the disclosed compounds have been prepared or isolated.

[0004] Etoricoxib and its hydrochloride salt obtained by the processes described in the '419 patent do not have satisfactory purity (Purity by HPLC: less than 90%) for pharmaceutical use.

[0005] PCT Publication Nos. WO01/992230 and WO 2005/085199 disclose various solid state forms of etoricoxib, processes for their preparation, and characterizes the solid state forms by powder X-ray diffraction (P-XRD) pattern.

[0006] There remains a need for novel solid state forms of etoricoxib salts and use thereof for preparing highly pure etoricoxib free base.

SUMMARY

[0007] In one aspect, provided herein are novel solid state forms of an etoricoxib salt, wherein the salt is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0008] In another aspect, etoricoxib salts in a crystalline form are provided. In yet another aspect, etoricoxib salts in an amorphous form are provided. In still another aspect, the solid state forms of etoricoxib salts exist in an anhydrous and/or solvent-free form or as a hydrate and/or a solvate form.

[0009] In another aspect, encompassed herein is a process for preparing a solid state form of an etoricoxib salt comprising contacting etoricoxib free base with an acid in a solvent under conditions sufficient to produce a reaction mass, and isolating the solid state form of etoricoxib acid addition salt, wherein the acid addition salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0010] In another aspect, encompassed herein is a process for preparing the highly pure etoricoxib free base or a pharmaceutically acceptable salt thereof by using the solid state forms of etoricoxib salts disclosed herein.

[001 1] In another aspect, provided herein is a method for treating a patient suffering from pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia,

synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondilitis, bursitis, burns, injuries, following surgical and dental procedures; comprising administering a solid state form of etoricoxib salt, or a pharmaceutical composition that comprises the solid state form of etoricoxib salt along with pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0012] In another aspect, provided herein is a pharmaceutical composition that comprises one of the solid state forms of etoricoxib salts disclosed herein, and one or more pharmaceutically acceptable excipients.

[0013] In still another aspect, provided herein is a pharmaceutical composition that comprises one of the solid state forms of etoricoxib salts made by the process disclosed herein, and one or more pharmaceutically acceptable excipients.

[0014] In still further aspect, encompassed is a process for preparing a pharmaceutical formulation comprising combining one of the solid state forms of etoricoxib salts disclosed herein with one or more pharmaceutically acceptable excipients.

[0015] In another aspect, the solid state forms of etoricoxib salts disclosed herein for use in the pharmaceutical compositions have a $_{D90}$ particle size of less than or equal to about 500 microns, specifically about 1 micron to about 300 microns, and most specifically about 10 microns to about 150 microns.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib oxalate salt.

[0017] Figure 2 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib oxalate salt.

[0018] Figure 3 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib succinate salt.

[0019] Figure 4 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib succinate salt.

[0020] Figure 5 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib fumarate salt.

[0021] Figure 6 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib fumarate salt.

[0022] Figure 7 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib besylate salt.

[0023] Figure 8 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib besylate salt.

[0024] Figure 9 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form I of etoricoxib hydrobromide salt.

[0025] Figure 10 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib hydrobromide salt.

[0026] Figure 11 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib glutamate salt.

[0027] Figure 12 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib glutamate salt.

[0028] Figure 13 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib sulfamate salt.

[0029] Figure 14 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib sulfamate salt.

[0030] Figure 15 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib benzoate salt.

[0031] Figure 16 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib benzoate salt.

[0032] Figure 17 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form I of etoricoxib cinnamate salt.

[0033] Figure 18 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib cinnamate salt.

[0034] Figure 19 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form II of etoricoxib cinnamate salt.

[0035] Figure 20 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form II of etoricoxib cinnamate salt.

[0036] Figure 21 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form I of etoricoxib salicylate salt.

[0037] Figure 22 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib salicylate salt.

[0038] Figure 23 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form II of etoricoxib salicylate salt.

[0039] Figure 24 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form II of etoricoxib salicylate salt.

[0040] Figure 25 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form III of etoricoxib salicylate salt.

[0041] Figure 26 is a characteristic differential scanning calorimetric (DSC) thermogram of crystalline form III of etoricoxib salicylate salt.

[0042] Figure 27 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form IV of etoricoxib salicylate salt.

[0043] Figure 28 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline etoricoxib tosylate salt.

[0044] Figure 29 is a characteristic powder X-ray diffraction (XRD) pattern of crystalline form II of etoricoxib hydrobromide salt.

DETAILED DESCRIPTION

[0045] Solid state forms of etoricoxib acid addition salts, except the hydrochloride salt, have not been reported, isolated, or characterized in the literature. The present inventors have surprisingly and unexpectedly found that some of the acid addition salts of 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine, i.e., etoricoxib salts, specifically, oxalate, succinate, fumarate, besylate, hydrobromide, glutamate, sulfamate, benzoate, cinnamate, salicylate and tosylate salts, can be isolated as solid state forms.

[0046] It has been surprisingly found that the solid state forms of etoricoxib salts disclosed herein, preferably the solid state forms of etoricoxib salicylate salt, are useful intermediates in the preparation of etoricoxib free base in high purity. The solid state forms of etoricoxib salts have good flow properties, and are stable at room temperature, enhanced temperature, at relative high humidities, and in aqueous media. The novel solid state forms of etoricoxib salts are suitable for formulating etoricoxib.

[0047] In the formulation of drug compositions, it is important for the active pharmaceutical ingredient to be in a form in which it can be conveniently handled and processed. Convenient handling is important not only from the perspective of obtaining a commercially viable manufacturing process, but also from the perspective of subsequent manufacture of pharmaceutical formulations (e.g., oral dosage forms such as tablets) comprising the active pharmaceutical ingredient.

[0048] Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical ingredient are important properties for a pharmaceutically active compound.

The active pharmaceutical ingredient, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g., its chemical composition, density, hygroscopicity and solubility. Thus, in the manufacture of commercially viable and pharmaceutically acceptable drug compositions, it is important, wherever possible, to provide the active pharmaceutical ingredient in a stable form.

[0049] New solid state forms of a pharmaceutical agent can further the development of formulations for the treatment of illnesses. For instance, solid forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, dissolution rate, bioavailability, chemical and physical stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products based on the compound.

[0050] The discovery of novel salts in solid state form of pharmaceutically useful compounds provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It also adds value to the material that a formulation scientist can use the same for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

[0051] According to one aspect, provided herein are novel solid state forms of etoricoxib salts, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0052] In one embodiment, the solid state forms of etoricoxib salts exist in a crystalline form. In another embodiment, the solid state forms of etoricoxib salts exist in an amorphous form. In another embodiment, the solid state forms of etoricoxib salts exist in an anhydrous and/or solvent-free form or as a hydrate and/or a solvate form. Such solvated or hydrated forms may be present as hemi-, mono-, sesqui-, di- or tri- solvates or hydrates. Solvates and hydrates may be formed as a result of the solvents used during the formation of the etoricoxib salts becoming embedded in the solid lattice structure. Because formation of the solvates and hydrates occurs during the preparation of etoricoxib salts, formation of a particular solvated or hydrated form depends greatly on the conditions and method used to prepare the salt. Solvents should be pharmaceutically acceptable.

[0053] In one embodiment, the solid state forms of etoricoxib salts have the following characteristics, wherein:

1) the solid state form of etoricoxib oxalate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 1;

ii) a powder X-ray diffraction pattern having peaks at about 11.43, 15.44, 16.6, 21.74, 22.56, 23.33, 24.25 and 27.06 ± 0.2 degrees 2-theta; and

iii) a powder X-ray diffraction pattern having additional peaks at about 11.96, 16.92, 17.11, 18.01, 19.09, 19.53, 25.3, 25.45, 26.11, 26.85, 27.94 and 29.29 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 2;

2) the solid state form of etoricoxib succinate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 3;

ii) a powder X-ray diffraction pattern having peaks at about 6.28, 16.15, 17.53, 17.75, 19.46, 19.94, 20.49, 20.76, 21.36, 25.52, 26.07 and 31.45 ± 0.2 degrees 2-theta; and

iii) a powder X-ray diffraction pattern having additional peaks at about 6.76, 7.67, 12.35, 13.08, 13.60, 18.12, 21.03, 22.19, 23.31, 24.54, 27.38, 28.26, 28.56 and 30.61 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 4;

3) the solid state form of etoricoxib fumarate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 5;

ii) a powder X-ray diffraction pattern having peaks at about 17.7, 19.35, 20.32, 20.82, 21.29, 22.73, 25.70, 28.73 and 29.36 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 6.32, 6.69, 7.69, 12.46, 13.04, 13.48, 16.16, 18.29, 22.27, 23.14, 23.41, 24.66, 26.78, 27.07, 27.59, 28.20, 28.42 and 30.92 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 6;

4) the solid state form of etoricoxib besylate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 7;

ii) a powder X-ray diffraction pattern having peaks at about 11.19, 16.03, 16.64, 17.25, 17.98, 19.04, 19.39, 19.65, 20.98, 22.27, 24.08, 24.78, 25.16 and 25.32 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 11.0, 13.35, 13.85, 14.33, 15.47, 18.23, 21.38, 21.94, 22.58, 23.44, 25.63, 26.09, 29.33, 29.76, 30.68 and 33.59 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 8;

5) the solid state form of etoricoxib hydrobromide salt is a crystalline form, designated herein as etoricoxib hydrobromide crystalline form I, characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 9;
   ii) a powder X-ray diffraction pattern having peaks at about 10.77, 15.45, 16.21, 16.47, 19.19, 20.06, 20.76, 21.65, 21.89, 22.42, 23.33, 23.79, 24.36, 25.02, 25.47, 26.08, 30.21 and 32.1 1 ± 0.2 degrees 2-theta;
   iii) a powder X-ray diffraction pattern having additional peaks at about 5.34, 11.63, 13.33, 14.84, 16.83, 19.43, 26.34, 27.40, 30.68 and 31.71 ± 0.2 degrees 2-theta; and
   iv) a DSC thermogram substantially in accordance with Figure 10;
6) the solid state form of etoricoxib hydrobromide salt is a crystalline form, designated herein as etoricoxib hydrobromide crystalline form II, characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 29; and
   ii) a powder X-ray diffraction pattern having peaks at about 5.96, 8.81, 12.01, 12.44, 13.01, 14.20, 17.01, 17.39, 17.72, 18.79, 20.39, 21.12, 21.42, 24.67, 24.86 and 25.72 ± 0.2 degrees 2-theta;
7) the solid state form of etoricoxib glutamate salt is characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 11;
   ii) a powder X-ray diffraction pattern having peaks at about 9.32, 10.16, 12.86, 16.56, 17.50, 18.42, 20.47, 21.39 and 22.01 ± 0.2 degrees 2-theta;
   iii) a powder X-ray diffraction pattern having additional peaks at about 5.45, 10.65, 16.91, 23.02, 23.62, 24.36, 25.52, 26.29, 29.88, 30.97, 33.63 and 35.58 ± 0.2 degrees 2-theta; and
   iv) a DSC thermogram substantially in accordance with Figure 12;
8) the solid state form of etoricoxib sulfamate salt is characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 13;
   ii) a powder X-ray diffraction pattern having peaks at about 9.31, 12.84, 16.53, 18.42, 21.83, 22.05 and 26.30 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 5.44, 10.65, 16.85, 17.47, 21.47, 22.59, 23.61, 23.95, 24.42, 29.23, 29.87, 32.66 and 32.90 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 14;

9) the solid state form of etoricoxib benzoate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 15;

ii) a powder X-ray diffraction pattern having peaks at about 9.35, 15.14, 17.08, 18.70, 18.93, 19.32, 20.39, 21.72, 22.05, 24.77 and 27.64 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 10.09, 16.90, 17.25, 22.36, 22.83, 25.40, 26.12 and 26.61 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 16;

10) the solid state form of etoricoxib cinnamate salt is a crystalline form, designated herein as etoricoxib cinnamate crystalline form I, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 17;

ii) a powder X-ray diffraction pattern having peaks at about 11.39, 15.41, 16.01, 16.56, 17.96, 19.03, 19.43, 19.59, 21.70, 22.53, 23.29, 24.10, 25.31 and 27.03 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 11.93, 13.36, 14.28, 14.46, 16.88, 17.09, 17.30, 19.93, 20.96, 22.18, 22.96, 24.84, 26.06, 26.83, 27.89, 29.01, 29.26 and 29.60 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 18;

1 l) the solid state form of etoricoxib cinnamate salt is a crystalline form, designated herein as etoricoxib cinnamate crystalline form II, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 19;

ii) a powder X-ray diffraction pattern having peaks at about 10.89, 12.44, 12.94, 14.70, 16.64, 16.93, 17.17, 17.68, 18.76, 19.18, 20.37, 22.34, 24.70, 24.90, 25.18, 26.09, 27.1 1 and 28.65 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 8.79, 11.70, 15.24, 15.69, 19.58, 21.3, 21.53, 23.44, 23.80, 24.32, 26.72, 28.02, 30.59, 37.92 and 39.81 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 20;

12) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form I, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 21;

ii) a powder X-ray diffraction pattern having peaks at about 7.05, 8.55, 9.89, 13.20, 14.19, 15.04, 15.66, 18.59, 19.09, 19.48, 19.61, 19.93, 20.33, 21.16, 21.42, 22.50, 22.84, 24.0 and 27.08 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 16.09, 16.23, 20.70, 22.08, 23.21, 23.68, 25.10, 25.49, 25.96, 29.33, 29.78, 30.13, 30.7, 31.47 and 31.87 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 22;

13) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form II, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 23;

ii) a powder X-ray diffraction pattern having peaks at about 8.82, 9.16, 11.72, 12.45, 12.97, 14.73, 16.66, 17.01, 17.72, 18.79, 19.19, 20.40, 22.38, 23.48, 24.72, 24.89, 26.11, 26.78 and 27.12 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 12.13, 20.69, 21.35, 21.57, 23.85, 24.36, 26.62, 28.79, 29.42, 30.75, 33.11, 34.27 and 34.72 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 24;

14) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form III, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 25;

ii) a powder X-ray diffraction pattern having peaks at about 6.98, 8.83, 11.72, 12.12, 12.45, 12.97, 13.44, 14.74, 16.52, 16.71, 17.01, 17.75, 18.80, 19.21, 20.41, 22.39, 23.49, 24.72, 24.90, 26.11, 26.80 and 27.14 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 9.16, 9.65, 15.44, 18.06, 20.02, 20.67, 21.36, 21.56, 22.71, 23.87, 24.10, 24.37, 26.59, 28.30, 28.81, 29.26, 29.41 and 30.76 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 26; and

15) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form IV, characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 27;
   ii) a powder X-ray diffraction pattern having peaks at about 10.90, 14.24, 16.25 and 25.21 ± 0.2 degrees 2-theta;
16) the solid state form of etoricoxib tosylate salt is characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 28;
   ii) a powder X-ray diffraction pattern having peaks at about 11.83, 12.81, 14.93, 15.10, 15.52, 16.61, 16.86, 17.78, 18.53, 18.70, 18.93, 19.30, 20.65, 23.71 and 25.65 ± 0.2 degrees 2-theta;
   iii) a powder X-ray diffraction pattern having additional peaks at about 9.18, 10.61, 13.04, 15.90, 19.52, 19.77, 20.14, 20.38, 22.34, 23.22, 23,46, 23.97, 25.88, 26.40, 26.58, 26.96, 29.83, 29.98, 31.66, 34.67, 37.52, 38.15 and 38.39 ± 0.2 degrees 2-theta.

[0054] The solid state forms of etoricoxib salts are stable, consistently reproducible, and are particularly suitable for bulk preparation and handling. Moreover, the solid state forms of etoricoxib salts are useful intermediates in the preparation of etoricoxib free base or a pharmaceutically acceptable salt thereof in high purity.

[0055] According to another aspect, there is provided a process for the preparation of a solid state form of an etoricoxib salt, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt, comprising:

a) providing a solution or a suspension of etoricoxib free base in a first solvent, wherein the first solvent is selected from the group consisting of toluene, xylene, ethyl acetate, methanol, ethanol, n-propanol, isopropyl alcohol, acetone, water, n-hexane, methylene chloride, acetonitrile, and mixtures thereof;
b) combining the solution or suspension obtained in step-(a) with an acid to produce a first reaction mass containing an etoricoxib acid addition salt, wherein the acid is selected from the group consisting of oxalic acid, succinic acid, fumaric acid, benzenesulfonic acid, hydrobromic acid, glutamic acid, sulfamic acid, benzoic acid, cinnamic acid, salicylic acid, p-toluenesulfonic acid; and

c) optionally, adding a second solvent to the first reaction mass obtained in step-(b) to produce a second reaction mass, wherein the second solvent is selected from the group consisting of water, an alcohol, a ketone, and mixtures thereof; or

d) optionally, substantially removing the first solvent from the first reaction mass to produce a solid or a residue and followed by combining with a third solvent to produce a third reaction mass, wherein the third solvent is selected from the group consisting of an aliphatic hydrocarbon, an ester, a nitrile, and mixtures thereof;

e) isolating and/or recovering the solid state form of etoricoxib salt from the reaction mass obtained in step-(b), (c) or (d).

[0056] The solid state form of etoricoxib salt obtained by the process disclosed herein is further optionally converted into highly pure etoricoxib free base by treating the solid state form of etoricoxib salt with a base in a suitable solvent as per the process disclosed hereinafter.

[0057] The process can produce solid state forms of etoricoxib salts in substantially pure form.

[0058] The term "substantially pure solid state form of etoricoxib salt" refers to the solid state form of etoricoxib salt having a purity of greater than about 98 wt%, specifically greater than about 99 wt%, more specifically greater than about 99.5 wt%, and still more specifically greater than about 99.9 wt%. The purity is preferably measured by High Performance Liquid Chromatography (HPLC). For example, the purity of solid state form of etoricoxib salt obtained by the process disclosed herein can be about 98% to about 99.95%, or about 99% to about 99.99%, as measured by HPLC.

[0059] In one embodiment, the process disclosed herein provides stable solid state forms of etoricoxib salts. The term "stable solid state form" refers to stability of the solid state form under the standard temperature and humidity conditions of testing of pharmaceutical products, wherein the stability is indicated by preservation of the original solid state form form.

[0060] In one embodiment, the first solvent used in step-(a) is selected from the group consisting of toluene, ethyl acetate, isopropyl alcohol, acetone, n-hexane, methylene chloride, acetonitrile, and mixtures thereof.

[0061] Step-(a) of providing a first solution of etoricoxib free base includes dissolving etoricoxib free base in the first solvent, or obtaining an existing solution from a previous processing step.

[0062] In one embodiment, the etoricoxib is dissolved in the solvent at a temperature of above about 20°C, specifically at about 25°C to about 100°C, and more specifically at about 40°C to about 80°C.

[0063] In another embodiment, step-(a) of providing a suspension of etoricoxib free base includes suspending etoricoxib free base in the first solvent while stirring at a temperature of about 0°C to the reflux temperature of the solvent used. In one embodiment, the suspension is stirred at a temperature of about 20°C to about 100°C for at least 30 minutes and more specifically at a temperature of about 40°C to about 80°C for about 1 hour to about 10 hours.

[0064] In another embodiment, the solution or suspension in step-(a) is prepared by reacting l-(6-methylpyridin-3-yl)-2-[4-(methylsulfonyl)phenyl]ethanone with 3-amino-2-chloroacrolein in a reaction inert solvent under suitable conditions to produce a reaction mass containing etoricoxib free base, followed by usual work up such as a washing, an extraction, an evaporation, a filtration, a pH adjustment, or a combination thereof. In one embodiment, the work-up includes dissolving, suspending or extracting the resulting etoricoxib in the first solvent at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at about 20°C to about 100°C, and more specifically at about 40°C to about 80°C.

[0065] In one embodiment, the solution or suspension obtained in step-(a) is stirred at a temperature of about 25°C to the reflux temperature of the solvent used for at least 15 minutes, and specifically at a temperature of about 40°C to the reflux temperature of the solvent used for about 20 minutes to about 8 hours.

[0066] As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

[0067] The acid in step-(b) may be used directly or in the form of a solution containing the acid and a solvent. The solvent used for dissolving the acid is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, amyl alcohol, isoamyl alcohol, hexanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, acetonitrile, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, methylene chloride, ethylene dichloride, chloroform, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

[0068] In one embodiment, the acid used in step-(b) is in a molar ratio of about 1.0 to 2.0 moles, specifically about 1.0 to 1.3 moles, per mole of etoricoxib free base.

[0069] Combining of the solution or suspension with acid in step-(b) is done in a suitable order, for example, the solution or suspension is added to the acid, or alternatively, the acid is added to the solution or suspension. The addition is, for example, carried out drop wise or in one portion or in more than one portion. The addition is specifically carried out at a temperature of above about 25°C, more specifically at about 40°C to about 80°C, and most specifically at about 50°C to about 70°C under stirring. After completion of the addition process, the resulting mass is stirred at a temperature of about 0°C to the reflux temperature of the solvent used for at least 10 minutes, specifically at about 15°C to about 110°C for about 20 minutes to about 10 hours, and more specifically at a temperature of about 20°C to about 30°C for about 30 minutes to about 4 hours to produce the first reaction mass.

[0070] The first reaction mass obtained in step-(b) is optionally subjected to carbon treatment or silica gel treatment. The carbon treatment or silica gel treatment is carried out by methods known in the art, for example, by stirring the solution with finely powdered carbon or silica gel at a temperature of below about 70°C for at least 15 minutes, specifically at a temperature of about 40°C to about 70°C for at least 30 minutes; and filtering the resulting mixture through hyflo to obtain a filtrate containing etoricoxib acid addition salt by removing charcoal or silica gel. Specifically, the finely powdered carbon is an active carbon. A specific mesh size of silica gel is 40-500 mesh, and more specifically 60-120 mesh.

[0071] In one embodiment, the second solvent used in step-(c) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, amyl alcohol, isoamyl alcohol, hexanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, and mixtures thereof; and more specifically, the second solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, acetone, and mixtures thereof.

[0072] In one embodiment, the third solvent used in step-(d) is selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, n-pentane, n-hexane, n-heptane, cyclohexane, cycloheptane, and mixtures thereof; and more specifically, the third solvent is a mixture of ethyl acetate and n-hexane.

[0073] The term "substantially removing" the solvent refers to at least 80%, specifically greater than about 85%, more specifically greater than about 90%, still more specifically greater than about 99%, and most specifically essentially complete (100%), removal of the solvent from the reaction mass.

[0074] Removal of solvent is accomplished, for example, by substantially complete evaporation of the solvent, concentrating the solution or distillation of solvent, under inert atmosphere.

[0075] In one embodiment, the solvent is removed by evaporation. Evaporation can be achieved at sub-zero temperatures by lyophilisation or freeze-drying techniques. The solution may also be completely evaporated in, for example, a pilot plant Rota vapor, a Vacuum Paddle Dryer or in a conventional reactor under vacuum above about 720 mm Hg by flash evaporation techniques by using an agitated thin film dryer ("ATFD"), or evaporated by spray drying to obtain a dry amorphous powder.

[0076] The distillation process can be performed at atmospheric pressure or reduced pressure. Specifically, the solvent is removed at a pressure of about 760 mm Hg or less, more specifically at about 400 mm Hg or less, still more specifically at about 80 mm Hg or less, and most specifically from about 30 to about 80 mm Hg.

[0077] Solvents can also be removed by spray-drying, in which a solution of etoricoxib salt is sprayed into the spray drier at the flow rate of 10 to 300 ml/hr, specifically 40 to 200ml/hr. The air inlet temperature to the spray drier used is about 30°C to about 150°C, specifically about 65°C to about 110°C and the outlet air temperature used is about 30°C to about 90°C.

[0078] Another suitable method is vertical agitated thin-film drying (or evaporation). Agitated thin film evaporation technology involves separating the volatile component using indirect heat transfer coupled with mechanical agitation of the flowing film under controlled conditions. In vertical agitated thin- film drying (or evaporation) (ATFD-V), the starting solution is fed from the top into a cylindrical space between a centered rotary agitator and an outside heating jacket. The rotor rotation agitates the downside-flowing solution while the heating jacket heats it.

[0079] The isolation of pure solid state form of etoricoxib salt in step-(e) is carried out by forcible crystallization, spontaneous crystallization, substantial removal of the solvent from the reaction mass, or a combination thereof.

[0080] Spontaneous crystallization refers to crystallization without the help of an external aid such as seeding, cooling etc., and forcible crystallization refers to crystallization with the help of an external aid.

[0081] Forcible crystallization may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, or a combination thereof.

[0082] The term "anti-solvent" refers to a solvent which when added to an existing solution of a substance reduces the solubility of the substance.

[0083] Exemplary anti-solvents include, but are not limited to, a hydrocarbon, an ether, and mixtures thereof. Specifically, the anti-solvent is selected from the group consisting of n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof; and most specifically diethyl ether, diisopropyl ether, and mixtures thereof.

[0084] In one embodiment, the crystallization is carried out by cooling the solution while stirring at a temperature of below 30°C for at least 10 minutes, specifically at about 0°C to about 25°C for about 30 minutes to about 20 hours.

[0085] The recovering in step-(e) is carried out by methods such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the solid state form of etoricoxib salt is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

[0086] The substantially pure solid state form of etoricoxib salt obtained by above process may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents. Drying can be carried out under reduced pressure until the residual solvent content reduces to the desired amount such as an amount that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines.

[0087] In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 80°C. The drying can be carried out for a desired time period that achieves the desired result, such as about 1 to 20 hours. Drying may also be carried out for shorter or longer periods of time depending on the product specifications. Temperatures and pressures will be chosen based on the volatility of the solvent being used and the foregoing should be considered as only a general guidance. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer and the like. Drying equipment selection is well within the ordinary skill in the art.

[0088] The purity of the solid state form of etoricoxib salt obtained by the process disclosed herein is greater than about 98%, specifically greater than about 99%, more specifically greater than about 99.9%, and most specifically greater than about 99.95% as

measured by HPLC. For example, the purity of the solid state form of etoricoxib salt can be about 99% to about 99.95%, or about 99.5% to about 99.99%.

[0089] Etoricoxib free base can be prepared in high purity by using the substantially pure solid state forms of etoricoxib salts disclosed herein by known methods or by the methods disclosed hereinafter.

[0090] According to another aspect, there is provided a process for preparing highly pure etoricoxib free base, comprising:

a) contacting solid state form of an etoricoxib salt with a base in a first solvent to provide a first reaction mass containing etoricoxib free base, wherein the first solvent is selected from the group consisting of water, an alcohol, a ketone, a nitrile, an ester, and mixtures thereof; and wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt;
b) extracting the etoricoxib free base with a second solvent to produce a second reaction mass, wherein the second solvent is selected from the group consisting of a chlorinated hydrocarbon, an ester, and mixtures thereof;
c) optionally, substantially removing the second solvent from the second reaction mass to produce a solid or a residue, followed by combining with a third solvent to produce a third reaction mass, wherein the third solvent is an alcohol, a ketone, a nitrile, an ether, a polar aprotic solvent, and mixtures thereof;
d) isolating and/or recovering the highly pure etoricoxib free base from the reaction mass obtained in step-(b) or (c), and optionally converting the pure etoricoxib free base obtained into a pharmaceutically acceptable salt thereof.

[0091] In one embodiment, the first solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, acetonitrile, ethyl acetate, isopropyl acetate, and mixtures thereof. Specifically, the first solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, ethyl acetate, and mixtures thereof; and a most specific first solvent is water.

[0092] In one embodiment, a preferred solid state form of etoricoxib salt used in step-(a) is etoricoxib salicylate salt.

[0093] In another embodiment, the base used in step-(a) is an organic or inorganic base. Exemplary organic bases include, but are not limited to, triethyl amine, dimethyl amine and tert-butyl amine.

[0094] In another embodiment, the base is an inorganic base. In yet another embodiment, the inorganic base is used in the form of an aqueous solution. Exemplary inorganic bases include, but are not limited to, aqueous ammonia; hydroxides, carbonates and bicarbonates of alkali or alkaline earth metals. Specific inorganic bases are aqueous ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate; and more specifically sodium bicarbonate, potassium bicarbonate, sodium carbonate and potassium carbonate.

[0095] The reaction in step-(a) is carried out at a temperature of about -25°C to about 100°C, specifically at a temperature of about 0°C to about 80°C, and more specifically at a temperature of about 25°C to about 50°C.

[0096] In one embodiment, the second solvent used in step-(b) is selected from the group consisting of methylene chloride, ethylene dichloride, chloroform, carbon tetrachloride, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, and mixtures thereof; and more specifically the second solvent is selected from the group consisting of ethyl acetate, isopropyl acetate, and mixtures thereof.

[0097] The term "substantially removing" the solvent refers to at least 30%, specifically greater than about 50%, more specifically greater than about 90%, still more specifically greater than about 99%, and most specifically essentially complete (100%), removal of the solvent from the solvent solution.

[0098] Removal of solvent in step-(c) is accomplished by the methods as described herein above.

[0099] In one embodiment, the third solvent used in step-(c) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, amyl alcohol, isoamyl alcohol, hexanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

[0100] Specifically, the third solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, acetonitrile, and mixtures thereof; and a more specific third solvent is isopropyl alcohol.

[0101] The pure etoricoxib free base obtained by the above process is isolated and/or recovered, and optionally further dried by the techniques as described above.

[0102] The purity of the etoricoxib free base obtained by the process disclosed herein is of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.95% as measured by HPLC. For example, the purity of the etoricoxib free base can be about 99% to about 99.95%, or about 99.5% to about 99.99%.

[0103] Further encompassed herein is the use of the solid state form of an etoricoxib salt for the manufacture of a pharmaceutical composition together with a pharmaceutically acceptable carrier, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0104] A specific pharmaceutical composition of the solid state form of etoricoxib salt is selected from a solid dosage form and an oral suspension.

[0105] In one embodiment, the solid state form of etoricoxib salt has a $_{D90}$ particle size of less than or equal to about 500 microns, specifically about 1 micron to about 300 microns, and most specifically about 10 microns to about 150 microns, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0106] According to another aspect, there is provided pharmaceutical compositions comprising the solid state form of etoricoxib salt and one or more pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0107] According to another aspect, there is provided pharmaceutical compositions comprising the solid state form of etoricoxib salt prepared according to process disclosed herein and one or more pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0108] According to another aspect, there is provided a process for preparing a pharmaceutical formulation comprising combining the solid state form of etoricoxib salt prepared according to the process disclosed herein with one or more pharmaceutically

acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0109] According to another aspect, there is provided a method for treating a patient suffering from pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondilitis, bursitis, burns, injuries, following surgical and dental procedures; comprising administering a pharmaceutical composition comprising the solid state form of etoricoxib salt along with pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[0110] Yet in another embodiment, pharmaceutical compositions comprise at least a therapeutically effective amount of solid state form of a etoricoxib salt, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt. Such pharmaceutical compositions may be administered to a mammalian patient in a dosage form, e.g., solid, liquid, powder, elixir, aerosol, syrups, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes or any other acceptable route of administration. Oral dosage forms include, but are not limited to, tablets, pills, capsules, syrup, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The solid state form of etoricoxib salt may also be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

[01 11] The pharmaceutical compositions 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.

[0112] In one embodiment, capsule dosage forms contain crystalline form of etoricoxib salt within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. Suitable enteric coating include 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, the coating agents 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.

[0113] 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 described herein may contain diluents such as cellulose-derived materials such as 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 such as mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[01 14] Other excipients 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.

INSTRUMENTAL DETAILS:

X-Ray Powder Diffraction (P-XRD):

[01 15] The X-Ray powder diffraction was measured by an X-ray powder Diffractometer equipped with CuKa-radiations (40kV, 40 mA) in wide-angle X-ray Diffractometer of BRUKER axs, D8 ADVANCE. The sample was analyzed using the following instrument parameters: measuring range= 3-45° 2-theta; step width=0.01579°; and measuring time per step=0.1 1 sec.

Differential Scanning Calorimetry (DSC):

[01 16] DSC (Differential Scanning Calorimetry) measurements were performed with a Differential Scanning Calorimeter (Diamond DSC, Perkin-Elmer) at a scan rate of 5°C per minute. The nitrogen gas purge was at 40 ml/min. The instrument was calibrated for temperature and heat flow using indium as standards. The samples were encapsulated in to closed aluminium pans without hole subsequently crimped to ensure a tight seal. Data acquisition and analysis were performed using pyris software.

[01 17] The following examples are given for the purpose of illustrating the present disclosure and should not be considered as limitation on the scope or spirit of the disclosure.

REFERENCE EXAMPLES

Reference Example 1

Preparation of crude Etoricoxib

Toluene (40 ml), propionic acid (25 ml), l-(6-methylpyridin-3-yl)-2-[4-(methylsulfonyl)phenyl]ethanone (5 g), 3-amino-2-chloroacrolein (5.4 g) and methanesulfonic acid (2.5 ml) were taken into a reaction flask, and the resulting mixture was heated at 100-1 10°C, followed by maintaining for 15 hours. Upon completion of the reaction, the reaction mass was cooled to 20-25°C, followed by the addition of water (25 ml) and ethyl acetate (50 ml). The pH of the reaction mass was adjusted to 7 to 7.5 using sodium bicarbonate solution (25%, 25 ml). The reaction mass was stirred and extracted with ethyl acetate (50 ml), followed by separation of the organic layer. The organic layer was washed with water (50 ml) twice, followed by carbon treatment [Carbon grade-Darco(D-60)]. The organic layer was heated at 50°C and filtered over a hyflo bed at 50°C. Ethyl acetate was distilled out under vacuum at 45-50°C to produce 5.5 g of crude etoricoxib as an oily mass (Purity by HPLC : 83.10%).

Reference Example 2

Preparation of Etoricoxib hydrochloride salt

Crude etoricoxib (10 g) was dissolved in ethyl acetate (40 ml) at 25-30°C, followed by adjusting the pH to 1.0 with 18% isopropanolic HC1 (5 ml). The resulting mass was stirred for 1-2 hours and the resulting mass was filtered, washed with ethyl acetate (10 ml) and then dried at 50-55°C for 1 hour to yield 10 g of etoricoxib hydrochloride salt (Purity by HPLC: 88.58%).

EXAMPLES

Example 1

Preparation of Crystalline form of Etoricoxib oxalate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C. Oxalic acid (0.45 g) was added to the resulting mass, followed by the addition of acetone (3 ml). The reaction mass was cooled to 20-25°C and maintained for 12 hours. The solid obtained was filtered, washed with toluene (2 ml) and then dried at 50-55°C for 1 hour to produce 1.15 g of crystalline etoricoxib oxalate salt (Purity by HPLC: 99.52%).

Example 2

Preparation of Crystalline form of Etoricoxib succinate

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of succinic acid (0.45 g). The reaction mass was cooled to 20-25°C and maintained for 2 hours. The solid obtained was filtered, washed with toluene (3 ml) and then dried at 50-55°C for 1 hour to yield 1.2 g of crystalline etoricoxib succinate (Purity by HPLC: 99.27%).

Example 3

Preparation of Crystalline form of Etoricoxib fumarate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of fumaric acid (0.40 g). The reaction mass was cooled to 20-25°C and maintained for 2 hours. The solid obtained was filtered, washed with toluene (3 ml) and then dried at 50-55°C for 1 hour to yield 1 g of crystalline etoricoxib fumarate salt (Purity by HPLC: 99.79%).

Example 4

Preparation of Crystalline form of Etoricoxib benzenesulfonate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of benzenesulfonic acid (0.50 g). Acetone (2ml) was added to the resulting mass, the reaction mass was cooled to 20-25°C and maintained for 2 hours. The solid obtained was filtered, washed with toluene (3 ml) and then dried at 50-55°C for 1 hour to yield 1.08 g of crystalline etoricoxib benzenesulfonate salt (Purity by HPLC: 99.64%).

Example 5

Preparation of Crystalline form of Etoricoxib hydrobromide salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of hydrobromic acid (49%, 1 ml). The reaction mass was cooled to 20-25°C and maintained for 2 hours. The solid obtained was filtered, washed with toluene (3 ml) and then dried at 50-55°C for 1 hour to yield 1.2 g of crystalline etoricoxib hydrobromide (Purity by HPLC: 95.93%).

Example 6

Preparation of crystalline form of Etoricoxib glutamate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of glutamic acid (0.5 g). The reaction mass was cooled to 20-25°C and maintained for 12 hours. The solid obtained was filtered, washed with toluene (5ml) and then dried at 50-55°C for 1 hour to yield 1.1 g of crystalline etoricoxib glutamate (Purity by HPLC: 95.24%).

Example 7

Preparation of Crystalline form of Etoricoxib sulfamate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of sulfamic acid (0.3 g). The reaction mass was cooled to 20-25°C and maintained for 12 hours. The solid obtained was filtered, washed with toluene (4 ml) and then dried at 50-55°C for 1 hour to yield 0.9 g of crystalline etoricoxib sulfamate (Purity by HPLC: 99.69%).

Example 8

Preparation of Crystalline form of Etoricoxib benzoate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of benzoic acid (0.45 g). The reaction mass was cooled to 20-25°C and maintained for 12 hours. Toluene was distilled out completely from the reaction mass, followed by the addition of n-hexane and ethyl acetate (6 ml). The resulting mixture was stirred for 2 hours, followed by cooling to 0-5°C. The solid obtained was filtered, washed with ethyl acetate (3 ml) and then dried at 50-55°C for 1 hour to yield 1.15 g of crystalline etoricoxib benzoate (Purity by HPLC: 99.69%).

Example 9

Preparation of Crystalline Form I of Etoricoxib cinnamate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of cinnamic acid (0.45 g). The reaction mass was cooled to 20-25°C and maintained for 12 hours. Toluene was distilled out completely from the reaction mass, followed by the addition of n-hexane and ethyl acetate (6 ml). The reaction mass was stirred for 2 hours and then cooled to 0-5°C. The solid obtained was filtered, washed with ethyl acetate (3 ml) and then dried at 50-55°C for 1 hour to yield 1.02 g of etoricoxib cinnamate crystalline form I (Purity by HPLC: 99.56%).

Example 10

Preparation of Crystalline Form I of Etoricoxib salicylate salt

Toluene (5 ml) and etoricoxib (1 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of salicylic acid (0.5 g). The reaction mass was cooled to 20-25°C and maintained for 2 hours. Toluene was distilled out completely from the reaction mass, followed by the addition of n-hexane (5 ml) and ethyl acetate (6 ml). The reaction mass was stirred for 2 hours and cooled to 0-5°C. The solid obtained was filtered, washed with ethyl acetate (3 ml) and then dried at 50-55°C for 1 hour to yield 1.13 g of etoricoxib salicylate crystalline form I (Purity by HPLC: 99.85%).

Example 11

Preparation of Crystalline Form II of Etoricoxib salicylate salt

Ethyl acetate (5 ml) and etoricoxib (1 g) were taken into a reaction flask at 20-25°C, followed by the addition of salicylic acid (0.5 g) and maintaining for 2 hours. The solid obtained was filtered, washed with ethyl acetate (2 ml) and then dried at 50-55°C for 1 hour to yield 1.08 g of etoricoxib salicylate crystalline form II (Purity by HPLC: 99.75%).

Example 12

Preparation of Crystalline Form III of Etoricoxib salicylate salt

Isopropyl alcohol (5 ml) and etoricoxib (1 g) were taken into a reaction flask at 20-25°C, followed by the addition of salicylic acid (0.5 g) and maintaining for 2 hours. The solid obtained was filtered, washed with isopropyl alcohol (2 ml) and then dried at 50-55°C for 1 hour to yield 1.1 g of etoricoxib salicylate crystalline form III (Purity by HPLC: 99.65%).

Example 13

Preparation of Crystalline form of Etoricoxib Tosylate

Toluene (3.6 ml), acetone (1.4 ml) and etoricoxib (0.5 g) were taken into a reaction flask, the mixture was heated at 50-55°C, followed by the addition of p-toluenesulfonic acid (0.5 g). The reaction mass was cooled to 20-25°C, maintained for 24 hours and further cooled to 0-5°C for 3 hours. The solid obtained was filtered, washed with toluene (2 ml) and then dried at 50-55°C for 1 hour to yield 0.35 g of crystalline etoricoxib tosylate (Purity by HPLC: 99.54%).

Example 14

Preparation of Crystalline Form I of Etoricoxib Salicylate salt

Crude etoricoxib (1 g, the oil obtained in reference example 1), toluene (5 ml) and salicylic acid (0.48 g) were taken into a reaction flask and the mixture was heated at 50-55°C. The resulting mass was cooled to 20-25°C and maintained for 12 hours. Toluene was distilled out completely from the resulting mass, followed by the addition of n-hexane (5 ml) and ethyl acetate (5 ml). The reaction mass was cooled to 0-5°C and maintained for 2 hours. The reaction mass was filtered, washed with ethyl acetate and then dried at 50-55°C for 1 hour to yield 0.90 g of etoricoxib salicylate crystalline form I (Purity by HPLC: 98.50%).

Example 15

Preparation of Crystalline Form II of Etoricoxib Salicylate salt

Crude etoricoxib (1 g, the oil obtained in reference example 1), acetone (5 ml) and salicylic acid (0.48 g) were taken into a reaction flask and the mixture was heated at 45-50°C. The resulting mass was cooled to 20-25°C and maintained for 12 hours. The reaction mass was cooled to 0-5°C and maintained for 2 hours. The reaction mass was filtered, washed with acetone and then dried at 50-55°C for 1 hour to yield 0.80 g of etoricoxib salicylate crystalline form II (Purity by HPLC: 99.13%).

Example 16

Preparation of Crystalline Form II of Etoricoxib salicylate salt

The process as described in the above example 14 was repeated by using ethyl acetate as a solvent in place of n-hexane and ethyl acetate mixture (Yield: 0.85 g, Purity by HPLC: 98.54%).

Example 17

Preparation of Crystalline Form II of Etoricoxib salicylate salt

The process as described in the above example 14 was repeated by using acetonitrile as a solvent in place of n-hexane and ethyl acetate mixture (Yield: 1 g, Purity by HPLC: 99.12%).

Example 18

Preparation of Crystalline Form II of Etoricoxib salicylate salt

The process as described in the above example 14 was repeated by using acetone as a solvent in place of n-hexane and ethyl acetate mixture (Yield: 0.72 g, Purity by HPLC: 99.26%).

Example 19

Preparation of Crystalline Form II of Etoricoxib salicylate salt

The process as described in the above example 14 was repeated by using isopropyl alcohol as a solvent in place of n-hexane and ethyl acetate mixture (Yield: 0.90 g, Purity by HPLC: 98.59%).

Example 20

Preparation of Crystalline Form II of Etoricoxib salicylate salt

The process as described in the above example 15 was repeated by using methylene dichloride as a solvent in place of n-hexane and ethyl acetate mixture (Yield: 0.90 g, Purity by HPLC: 97.78%).

Example 21

Preparation of Crystalline form of Etoricoxib oxalate salt

Crude etoricoxib (1 g, the oil obtained in reference example 1), toluene (4 ml), oxalic acid (0.45 g) and acetone (3 ml) were taken into a reaction flask at 20-25°C, followed by heating the mixture at 50-55°C. The resulting mass was cooled at 20-25°C and maintained for 10-12 hours. The reaction mass was filtered, washed with toluene (2 ml) and then dried at 50-55°C for 1 hour to yield 1.15 g of crystalline etoricoxib oxalate salt (Purity by HPLC: 93.57%).

Example 22

Preparation of Crystalline Form II of Etoricoxib cinnamate salt

The process as described in the above example 21 was repeated by using cinnamic acid instead of oxalic acid, and ethyl acetate instead of toluene for washing the reaction mass after filtering (Yield: 1.02 g, Purity by HPLC: 97.48%).

Example 23

Purification of Etoricoxib salicylate salt

Crude etoricoxib salicylate salt (10 g, HPLC purity: 99.15%; content of impurities: Ό.45 RRT' impurity: 0.25%, Ό.71 RRT' impurity: 0.40%) was dissolved in acetonitrile (120 ml) at 70-75°C. The solution was charcolized (Darco G60) at 70-75°C, filtered through a hyflo bed and washed with acetonitrile (20 ml) at 70-75°C. Acetonitrile was distilled off from the resulting filtrate at 50°C under reduced pressure up to 1/3 of its original volume. The reaction mixture was cooled to 0-5°C and stirred for 2 hours. The resulting product was filtered and washed with acetonitrile (20 ml). The resulting solid was dried under vacuum at 50-55°C to give 8.5 g of pure etoricoxib salicylate (HPLC Purity: 99.65%>; content of impurities: Ό.45 RRT' impurity: 0.11%; and Ό.71 RRT' impurity: 0.20%).

Example 24

Isolation of Etoricoxib free base using Etoricoxib salicylate salt

Pure etoricoxib salicylate salt (10 g, HPLC purity: 99.86%>) was suspended in water (20 ml), followed by adjusting the pH to 8.5 to 9.0 with aqueous ammonia (20 ml) and extracting the product with ethyl acetate (3 x 40 ml). The resulting organic layer was charcolized (Darco G60) at 25-35°C, filtered through a hyflo bed and washed with ethyl acetate (20 ml) at 25-35°C. Ethyl acetate was distilled off completely from the resulting filtrate at 45-50°C under reduced pressure, followed by stripping off the ester solvent with isopropanol and then dissolving the resulting residual mass in isopropanol (120 ml) at 50-60°C. The reaction mixture was cooled to 0-5°C and stirred for 2 hours. The resulting product was filtered and washed with isopropanol (20 ml). The resulting solid was dried under vacuum at 50-55°C to give 6 g of pure etoricoxib (HPLC Purity: 99.96%>).

Example 25

Preparation of Crystalline Form III of Etoricoxib salicylate salt

Crude etoricoxib (3.5 g, the oily mass obtained according to reference example 1) was dissolved in toluene (10ml) at 45-50°C, followed by the addition of salicylic acid (2.6 g) at 45-50°C. The resulting mass was cooled to ambient temperature, the resulting solid was

filtered and then washed the solid with toluene (3.5 ml). The resulting solid was dried under vacuum at 50-55°C to give 4 g of etoricoxib salicylate (HPLC Purity: 95.40%).

Example 26

Preparation of Crystalline Form II of Etoricoxib hydrobromide salt

Crude etoricoxib (3.5 g, the oily mass obtained according to reference example 1) was dissolved in isopropanol (10 ml) at 25-30°C, followed by the addition of aqueous hydrobromic acid (2 ml) at 25-30°C. The resulting mass was stirred for 2 to 3 hours, the resulting solid was filtered and then washed with isopropanol (3.5 ml). The resulting solid was dried under vacuum at 50-55°C to give 1.5 g of etoricoxib hydrobromide crystalline Form II (HPLC Purity: 98.10%).

[01 18] Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

[0119] The term "solid state form of etoricoxib salt disclosed herein" includes crystalline forms, amorphous form, hydrated, and solvated forms of etoricoxib salt.

[0120] The term "crystalline form" refers to a crystal modification that can be characterized by analytical methods such as X-ray powder diffraction, IR-spectroscopy, differential scanning calorimetry (DSC) or by its melting point.

[0121] The term "pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally non-toxic and is not biologically undesirable, and includes that which is acceptable for veterinary use and/or human pharmaceutical use.

[0122] The term "pharmaceutical composition" is intended to encompass a drug product including the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients. Accordingly, the pharmaceutical compositions encompass any composition made by admixing the active ingredient, active ingredient dispersion or composite, additional active ingredient(s), and pharmaceutically acceptable excipients.

[0123] 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.

[0124] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host 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.

[0125] 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 include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such materials known to those of ordinary skill in the art.

[0126] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a formulation. 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.

[0127] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, polyvinylpyrrolidone, compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, pregelatinized starch, starch, polyethylene glycol, guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC(™) F68, PLURONIC(™) F127), collagen, albumin, celluloses in non-aqueous solvents, polypropylene glycol, polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, polyethylene oxide, microcrystalline cellulose, combinations thereof and other material known to those of ordinary skill in the art.

[0128] 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 solid dosage formulations. 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.

[0129] The term "glidant" as used herein is intended to mean agents used in solid dosage 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.

[0130] The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. 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.

[0131] The term "disintegrant" as used herein is intended to mean a compound used in solid dosage formulations 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, 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.

[0132] 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., macrogo1ethers 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, and polyvinylpyrrolidone (PVP).

[0133] The term "micronization" used herein means a process or method by which the size of a population of particles is reduced.

[0134] As used herein, the term "micron" or "μιη" both are equivalent and refer to "micrometer" which is $lxlO^{-6}$ meter.

[0135] As used herein, "crystalline particles" means any combination of single crystals, aggregates and agglomerates.

[0136] As used herein, "Particle Size Distribution (P.S.D)" means the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction in Malvern Master Sizer 2000 equipment or its equivalent.

[0137] The important characteristics of the PSD are the (D90), which is the size, in microns, below which 90% of the particles by volume are found, and the (D_{50}), which is the size, in microns, below which 50%> of the particles by volume are found. Thus, a D_{9_0} or d(0.9) of less than 300 microns means that 90 volume-percent of the particles in a composition have a diameter less than 300 microns.

[0138] All ranges disclosed herein are inclusive and combinable. While the invention has been described with reference to a preferred embodiment, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the appended claims.

We claim:

1. Solid state form of a salt of 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine (etoricoxib salt), wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.
2. The solid state form of etoricoxib salt of claim 1, which is in a crystalline form or in an amorphous form, and wherein the solid state form is anhydrous and/or solvent-free form, or a hydrate and/or a solvate form.
3. The solid state form of etoricoxib salt of claim 1, having the following characteristics, wherein:
   1) the solid state form of etoricoxib oxalate salt is characterized by one or more of the following properties:
      i) a powder X-ray diffraction pattern substantially in accordance with Figure 1;
      ii) a powder X-ray diffraction pattern having peaks at about 11.43, 15.44, 16.6, 21.74, 22.56, 23.33, 24.25 and 27.06 ± 0.2 degrees 2-theta; and
      iii) a powder X-ray diffraction pattern having additional peaks at about 11.96, 16.92, 17.11, 18.01, 19.09, 19.53, 25.3, 25.45, 26.11, 26.85, 27.94 and 29.29 ± 0.2 degrees 2-theta; and
      iv) a DSC thermogram substantially in accordance with Figure 2;
   2) the solid state form of etoricoxib succinate salt is characterized by one or more of the following properties:
      i) a powder X-ray diffraction pattern substantially in accordance with Figure 3;
      ii) a powder X-ray diffraction pattern having peaks at about 6.28, 16.15, 17.53, 17.75, 19.46, 19.94, 20.49, 20.76, 21.36, 25.52, 26.07 and 31.45 ± 0.2 degrees 2-theta; and
      iii) a powder X-ray diffraction pattern having additional peaks at about 6.76, 7.67, 12.35, 13.08, 13.60, 18.12, 21.03, 22.19, 23.31, 24.54, 27.38, 28.26, 28.56 and 30.61 ± 0.2 degrees 2-theta; and
      iv) a DSC thermogram substantially in accordance with Figure 4;
   3) the solid state form of etoricoxib fumarate salt is characterized by one or more of the following properties:
      i) a powder X-ray diffraction pattern substantially in accordance with Figure 5;
      ii) a powder X-ray diffraction pattern having peaks at about 17.7, 19.35, 20.32, 20.82, 21.29, 22.73, 25.70, 28.73 and 29.36 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 6.32, 6.69, 7.69, 12.46, 13.04, 13.48, 16.16, 18.29, 22.27, 23.14, 23.41, 24.66, 26.78, 27.07, 27.59, 28.20, 28.42 and 30.92 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 6;

4) the solid state form of etoricoxib besylate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 7;

ii) a powder X-ray diffraction pattern having peaks at about 11.19, 16.03, 16.64, 17.25, 17.98, 19.04, 19.39, 19.65, 20.98, 22.27, 24.08, 24.78, 25.16 and 25.32 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 11.0, 13.35, 13.85, 14.33, 15.47, 18.23, 21.38, 21.94, 22.58, 23.44, 25.63, 26.09, 29.33, 29.76, 30.68 and 33.59 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 8;

5) the solid state form of etoricoxib hydrobromide salt is a crystalline form, designated herein as etoricoxib hydrobromide crystalline form I, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 9;

ii) a powder X-ray diffraction pattern having peaks at about 10.77, 15.45, 16.21, 16.47, 19.19, 20.06, 20.76, 21.65, 21.89, 22.42, 23.33, 23.79, 24.36, 25.02, 25.47, 26.08, 30.21 and 32.11 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 5.34, 11.63, 13.33, 14.84, 16.83, 19.43, 26.34, 27.40, 30.68 and 31.71 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 10;

6) the solid state form of etoricoxib hydrobromide salt is a crystalline form, designated herein as etoricoxib hydrobromide crystalline form II, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 29; and

ii) a powder X-ray diffraction pattern having peaks at about 5.96, 8.81, 12.01, 12.44, 13.01, 14.20, 17.01, 17.39, 17.72, 18.79, 20.39, 21.12, 21.42, 24.67, 24.86 and 25.72 ± 0.2 degrees 2-theta;

7) the solid state form of etoricoxib glutamate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 11;

ii) a powder X-ray diffraction pattern having peaks at about 9.32, 10.16, 12.86, 16.56, 17.50, 18.42, 20.47, 21.39 and 22.01 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 5.45, 10.65, 16.91, 23.02, 23.62, 24.36, 25.52, 26.29, 29.88, 30.97, 33.63 and 35.58 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 12;

8) the solid state form of etoricoxib sulfamate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 13;

ii) a powder X-ray diffraction pattern having peaks at about 9.31, 12.84, 16.53, 18.42, 21.83, 22.05 and 26.30 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 5.44, 10.65, 16.85, 17.47, 21.47, 22.59, 23.61, 23.95, 24.42, 29.23, 29.87, 32.66 and 32.90 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 14;

9) the solid state form of etoricoxib benzoate salt is characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 15;

ii) a powder X-ray diffraction pattern having peaks at about 9.35, 15.14, 17.08, 18.70, 18.93, 19.32, 20.39, 21.72, 22.05, 24.77 and 27.64 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 10.09, 16.90, 17.25, 22.36, 22.83, 25.40, 26.12 and 26.61 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 16;

10) the solid state form of etoricoxib cinnamate salt is a crystalline form, designated herein as etoricoxib cinnamate crystalline form I, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 17;

ii) a powder X-ray diffraction pattern having peaks at about 11.39, 15.41, 16.01, 16.56, 17.96, 19.03, 19.43, 19.59, 21.70, 22.53, 23.29, 24.10, 25.31 and 27.03 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 11.93, 13.36, 14.28, 14.46, 16.88, 17.09, 17.30, 19.93, 20.96, 22.18, 22.96, 24.84, 26.06, 26.83, 27.89, 29.01, 29.26 and 29.60 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 18;

11) the solid state form of etoricoxib cinnamate salt is a crystalline form, designated herein as etoricoxib cinnamate crystalline form II, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 19;

ii) a powder X-ray diffraction pattern having peaks at about 10.89, 12.44, 12.94, 14.70, 16.64, 16.93, 17.17, 17.68, 18.76, 19.18, 20.37, 22.34, 24.70, 24.90, 25.18, 26.09, 27.1 1 and 28.65 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 8.79, 11.70, 15.24, 15.69, 19.58, 21.3, 21.53, 23.44, 23.80, 24.32, 26.72, 28.02, 30.59, 37.92 and 39.81 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 20;

12) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form I, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 2 1;

ii) a powder X-ray diffraction pattern having peaks at about 7.05, 8.55, 9.89, 13.20, 14.19, 15.04, 15.66, 18.59, 19.09, 19.48, 19.61, 19.93, 20.33, 21.16, 21.42, 22.50, 22.84, 24.0 and 27.08 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 16.09, 16.23, 20.70, 22.08, 23.21, 23.68, 25.10, 25.49, 25.96, 29.33, 29.78, 30.13, 30.7, 31.47 and 31.87 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 22;

13) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form II, characterized by one or more of the following properties:

i) a powder X-ray diffraction pattern substantially in accordance with Figure 23;

ii) a powder X-ray diffraction pattern having peaks at about 8.82, 9.16, 11.72, 12.45, 12.97, 14.73, 16.66, 17.01, 17.72, 18.79, 19.19, 20.40, 22.38, 23.48, 24.72, 24.89, 26.1 1, 26.78 and 27.12 ± 0.2 degrees 2-theta;

iii) a powder X-ray diffraction pattern having additional peaks at about 12.13, 20.69, 21.35, 21.57, 23.85, 24.36, 26.62, 28.79, 29.42, 30.75, 33.1 1, 34.27 and 34.72 ± 0.2 degrees 2-theta; and

iv) a DSC thermogram substantially in accordance with Figure 24;

14) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form III, characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 25;
   ii) a powder X-ray diffraction pattern having peaks at about 6.98, 8.83, 11.72, 12.12, 12.45, 12.97, 13.44, 14.74, 16.52, 16.71, 17.01, 17.75, 18.80, 19.21, 20.41, 22.39, 23.49, 24.72, 24.90, 26.11, 26.80 and 27.14 ± 0.2 degrees 2-theta;
   iii) a powder X-ray diffraction pattern having additional peaks at about 9.16, 9.65, 15.44, 18.06, 20.02, 20.67, 21.36, 21.56, 22.71, 23.87, 24.10, 24.37, 26.59, 28.30, 28.81, 29.26, 29.41 and 30.76 ± 0.2 degrees 2-theta; and
   iv) a DSC thermogram substantially in accordance with Figure 26; and
15) the solid state form of etoricoxib salicylate salt is a crystalline form, designated herein as etoricoxib salicylate crystalline form IV, characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 27;
   ii) a powder X-ray diffraction pattern having peaks at about 10.90, 14.24, 16.25 and 25.21 ± 0.2 degrees 2-theta;
16) the solid state form of etoricoxib tosylate salt is characterized by one or more of the following properties:
   i) a powder X-ray diffraction pattern substantially in accordance with Figure 28;
   ii) a powder X-ray diffraction pattern having peaks at about 11.83, 12.81, 14.93, 15.10, 15.52, 16.61, 16.86, 17.78, 18.53, 18.70, 18.93, 19.30, 20.65, 23.71 and 25.65 ± 0.2 degrees 2-theta;
   iii) a powder X-ray diffraction pattern having additional peaks at about 9.18, 10.61, 13.04, 15.90, 19.52, 19.77, 20.14, 20.38, 22.34, 23.22, 23,46, 23.97, 25.88, 26.40, 26.58, 26.96, 29.83, 29.98, 31.66, 34.67, 37.52, 38.15 and 38.39 ± 0.2 degrees 2-theta.

4. A process for the preparation of solid state form of etoricoxib salt of claim 1, comprising:
   a) providing a solution or a suspension of etoricoxib free base in a first solvent, wherein the first solvent is selected from the group consisting of toluene, xylene, ethyl acetate, methanol, ethanol, n-propanol, isopropyl alcohol, acetone, water, n-hexane, methylene chloride, acetonitrile, and mixtures thereof;
   b) combining the solution or suspension obtained in step-(a) with an acid to produce a first reaction mass containing an etoricoxib acid addition salt, wherein the acid is

selected from the group consisting of oxalic acid, succinic acid, fumaric acid, benzenesulfonic acid, hydrobromic acid, glutamic acid, sulfamic acid, benzoic acid, cinnamic acid, salicylic acid, p-toluenesulfonic acid; and

c) optionally, adding a second solvent to the first reaction mass obtained in step-(b) to produce a second reaction mass, wherein the second solvent is selected from the group consisting of water, an alcohol, a ketone, and mixtures thereof; or

d) optionally, substantially removing the first solvent from the first reaction mass to produce a solid or a residue and followed by combining with a third solvent to produce a third reaction mass, wherein the third solvent is selected from the group consisting of an aliphatic hydrocarbon, an ester, a nitrile, and mixtures thereof;

e) isolating and/or recovering the solid state form of etoricoxib salt from the reaction mass obtained in step-(b), (c) or (d).

5. The process of claim 4, wherein the first solvent used in step-(a) is selected from the group consisting of toluene, ethyl acetate, isopropyl alcohol, acetone, n-hexane, methylene chloride, acetonitrile, and mixtures thereof; wherein the second solvent used in step-(c) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, amyl alcohol, isoamyl alcohol, hexanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, and mixtures thereof; and wherein the third solvent used in step-(d) is selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, n-pentane, n-hexane, n-heptane, cyclohexane, cycloheptane, and mixtures thereof.

6. The process of claim 5, wherein the second solvent used in step-(c) is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, acetone, and mixtures thereof; and wherein the third solvent used in step-(d) is a mixture of ethyl acetate and n-hexane.

7. The process of claim 4, wherein the first reaction mass obtained in step-(b) is optionally subjected to carbon treatment or silica gel treatment; and wherein the isolation of pure solid state form of etoricoxib salt in step-(e) is carried out by forcible crystallization, spontaneous crystallization, substantial removal of the solvent from the reaction mass, or a combination thereof.

8. The process of claim 7, wherein the crystallization in step-(e) is carried out by cooling the solution while stirring at a temperature of about 0°C to about 25°C.

9. A process for preparing highly pure etoricoxib free base, comprising:

a) contacting solid state form of an etoricoxib salt with a base in a first solvent to provide a first reaction mass containing etoricoxib free base, wherein the first solvent is selected from the group consisting of water, an alcohol, a ketone, a nitrile, an ester, and mixtures thereof; and wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt;

b) extracting the etoricoxib free base with a second solvent to produce a second reaction mass, wherein the second solvent is selected from the group consisting of a chlorinated hydrocarbon, an ester, and mixtures thereof;

c) optionally, substantially removing the second solvent from the second reaction mass to produce a solid or a residue, followed by combining with a third solvent to produce a third reaction mass, wherein the third solvent is an alcohol, a ketone, a nitrile, an ether, a polar aprotic solvent, and mixtures thereof;

d) isolating and/or recovering the highly pure etoricoxib free base from the reaction mass obtained in step-(b) or (c), and optionally converting the pure etoricoxib free base obtained into a pharmaceutically acceptable salt thereof.

10. The process of claim 9, wherein the first solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, acetonitrile, ethyl acetate, isopropyl acetate, and mixtures thereof; wherein the second solvent used in step-(b) is selected from the group consisting of methylene chloride, ethylene dichloride, chloroform, carbon tetrachloride, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, and mixtures thereof; and wherein the third solvent used in step-(c) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, isobutanol, n-butanol, tert-butanol, amyl alcohol, isoamyl alcohol, hexanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, acetonitrile, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

11. The process of claim 10, wherein the first solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, ethyl acetate, and mixtures thereof; wherein the second solvent used in step-(b) is selected from the group consisting of ethyl acetate, isopropyl acetate, and mixtures thereof; and wherein the

third solvent used in step-(c) is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, acetonitrile, and mixtures thereof.

12. The process of claim 9, wherein the base used in step-(a) is selected from the group consisting of triethyl amine, dimethyl amine, tert-butyl amine, aqueous ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate; and wherein the reaction in step-(a) is carried out at a temperature of about -25°C to about 100°C.
13. The process of claim 12, wherein the base used in step-(a) is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, sodium carbonate and potassium carbonate; and wherein the reaction in step-(a) is carried out at a temperature of about 25°C to about 50°C.
14. The process of claim 9, wherein the solid state form of an etoricoxib salt used in step-(a) is etoricoxib salicylate salt.
15. A pharmaceutical composition comprising a solid state form of a etoricoxib salt and one or more pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.
16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is a solid dosage form, an oral suspension, a liquid, a powder, an elixir, an aerosol, a syrup, or an injectable solution.
17. A method for treating a patient suffering from pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondilitis, bursitis, burns, injuries, following surgical and dental procedures; comprising administering a pharmaceutical composition comprising the solid state form of etoricoxib salt along with pharmaceutically acceptable excipients, wherein the salt of etoricoxib is an oxalate salt, a succinate salt, a fumarate salt, a besylate salt, a hydrobromide salt, a glutamate salt, a sulfamate salt, a benzoate salt, a cinnamate salt, a salicylate salt or a tosylate salt.

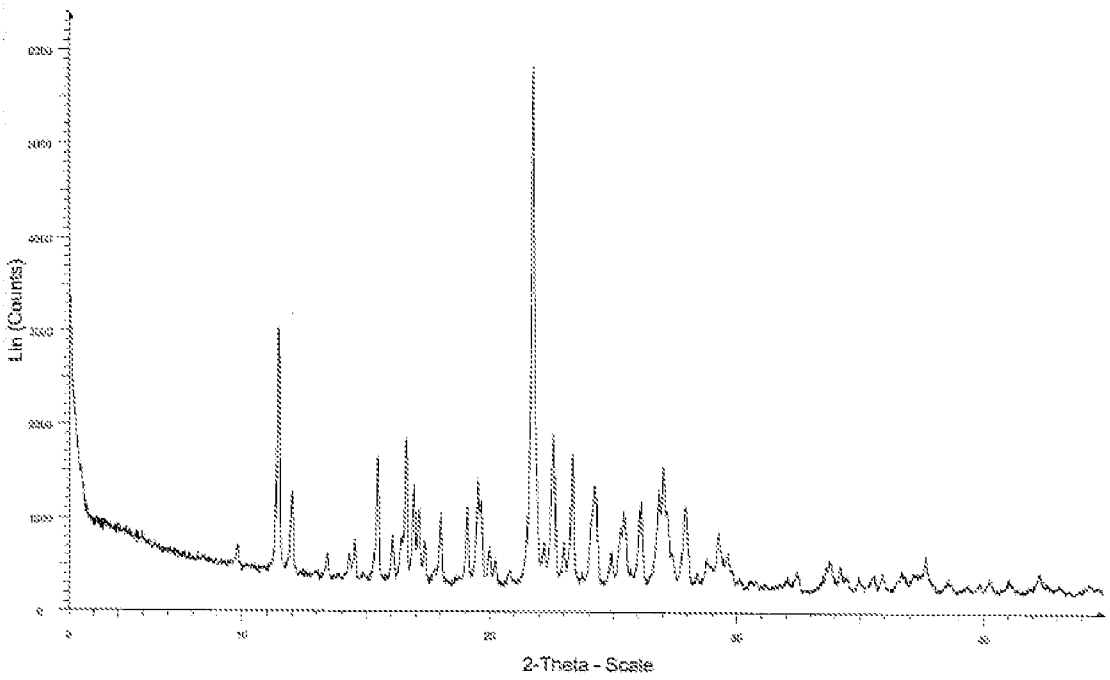


Figure 1: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib oxalate salt

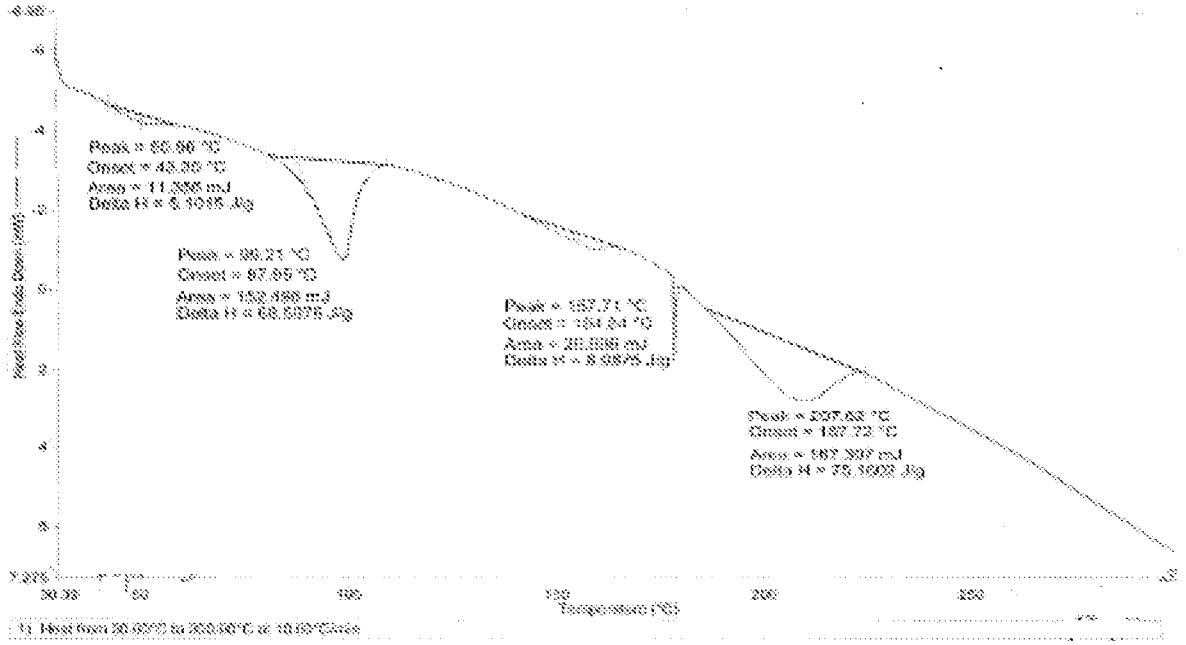


Figure 2: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib oxalate salt

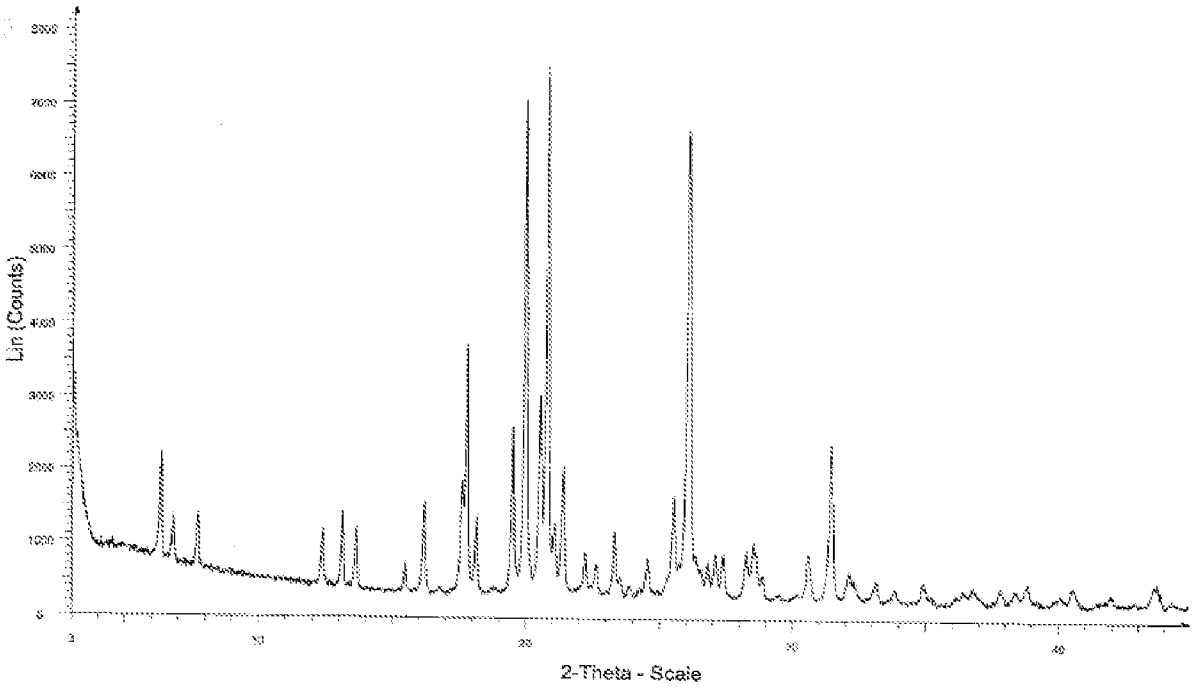


Figure 3: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib succinate salt.

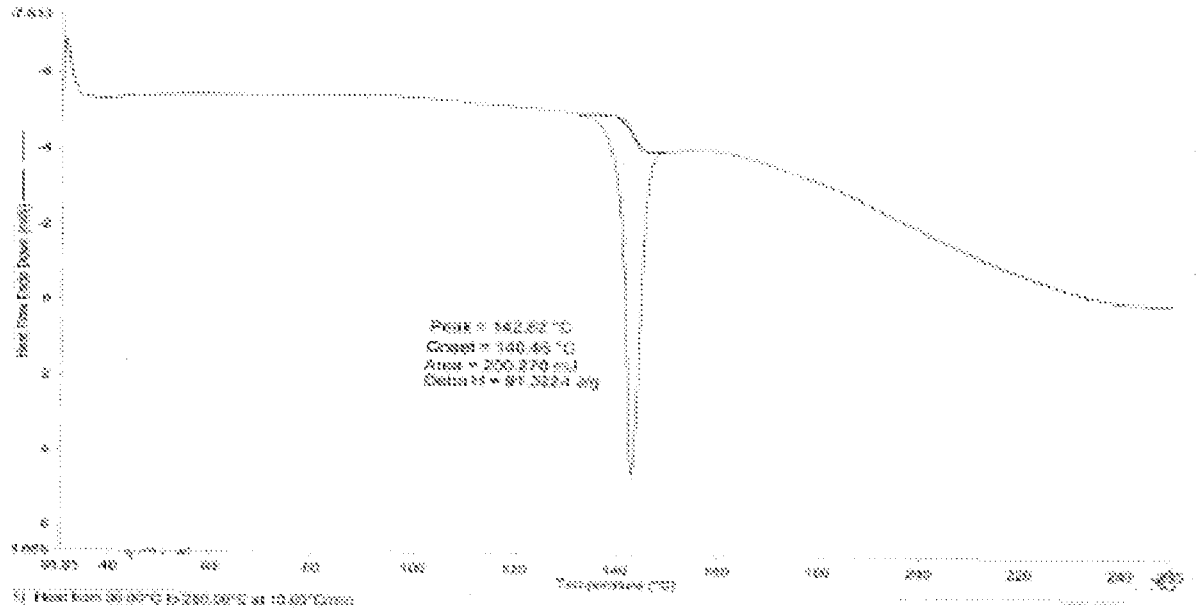


Figure 4: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib succinate salt

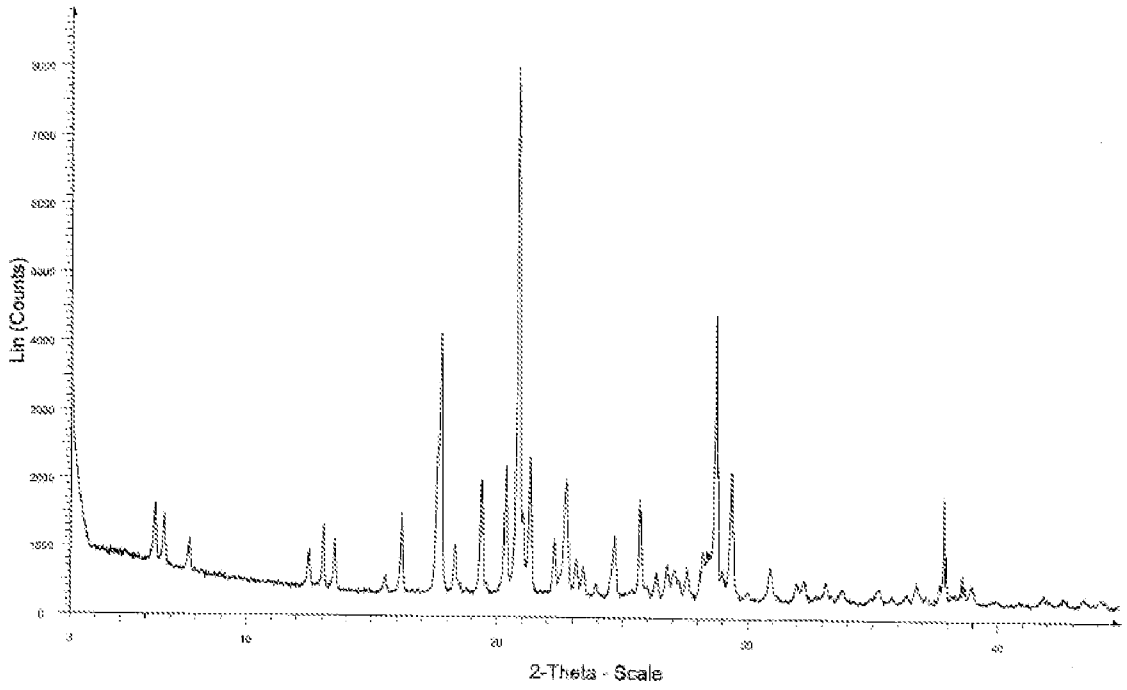


Figure 5: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib fumarate salt

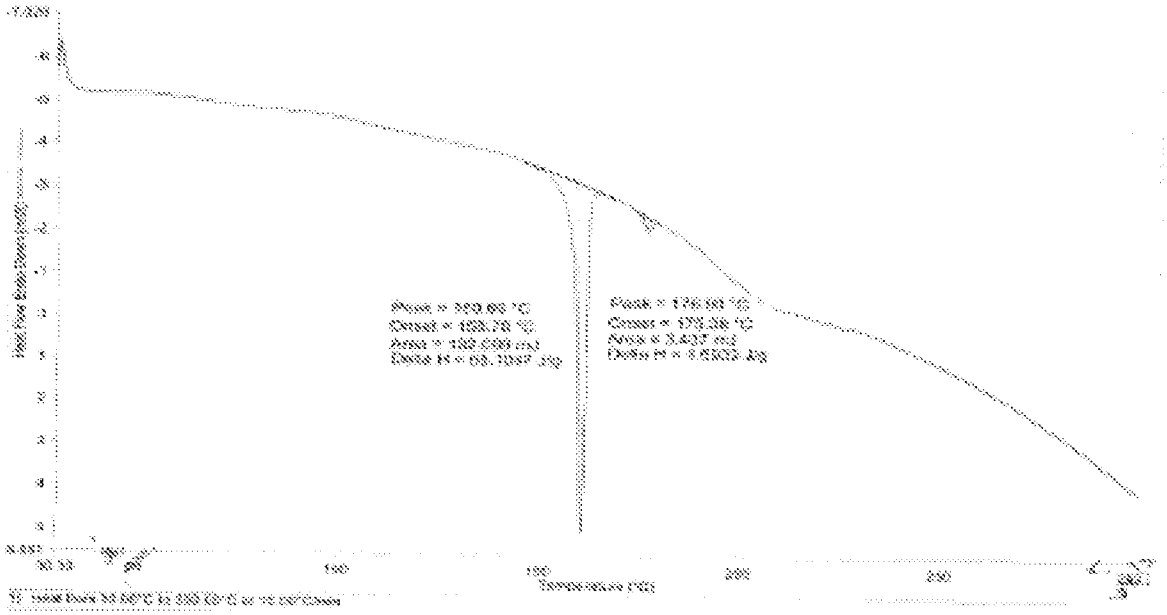


Figure 6: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib fumarate salt

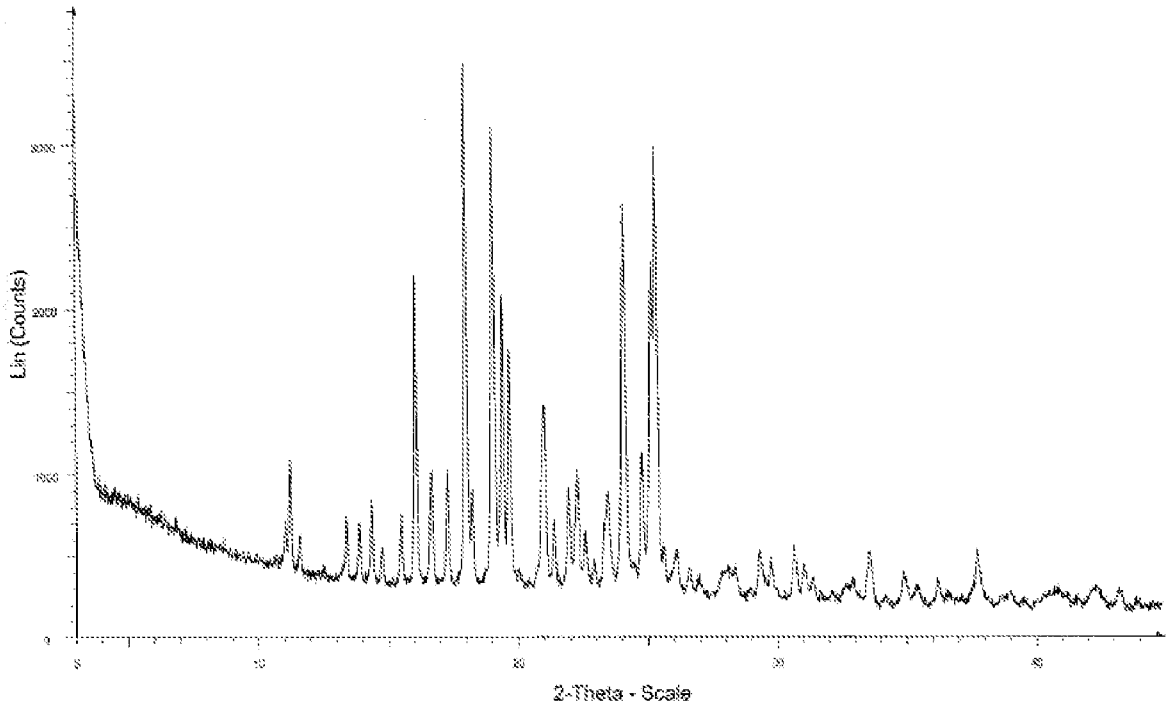


Figure 7: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib besylate salt

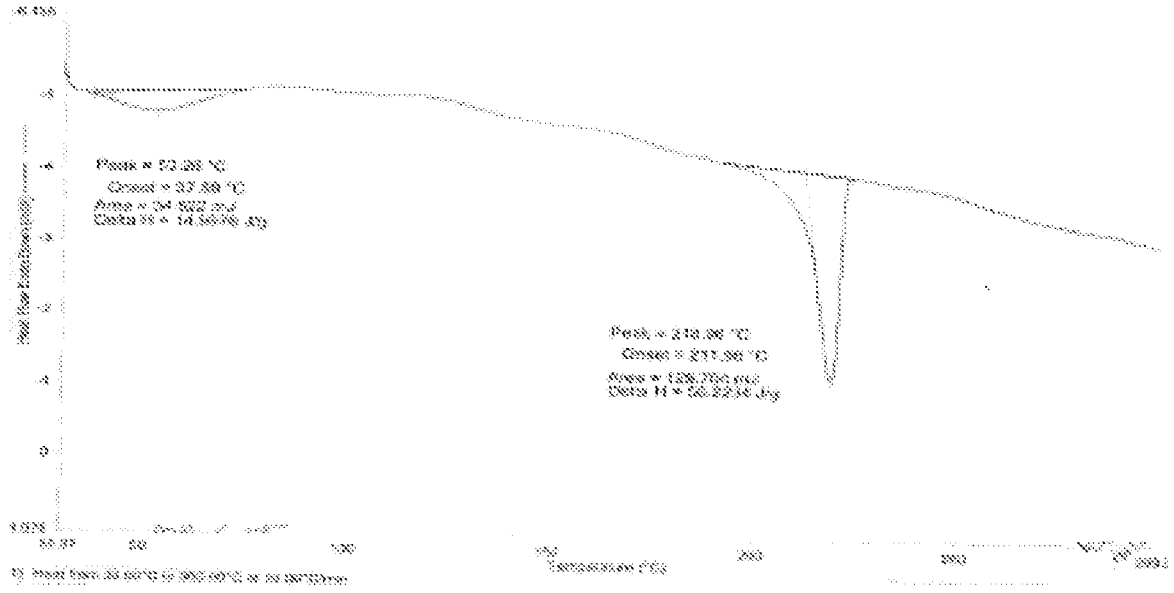


Figure 8: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib besylate salt

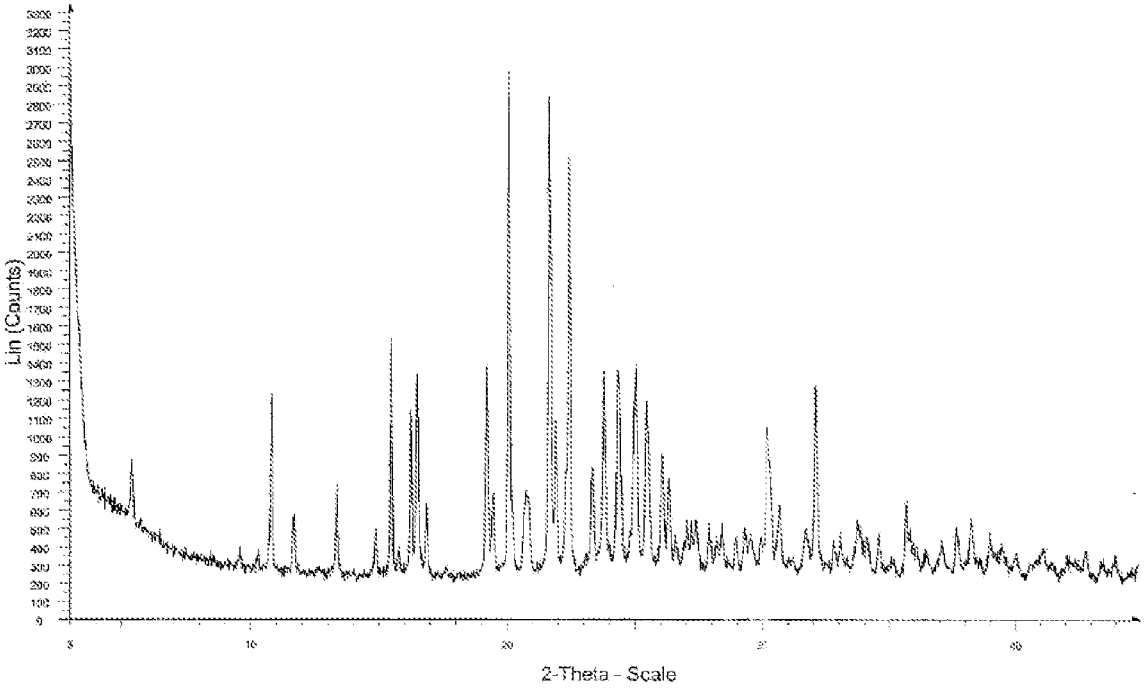


Figure 9: Powder X-ray Diffraction (XRD) pattern of crystalline form I of etoricoxib hydrobromide salt.

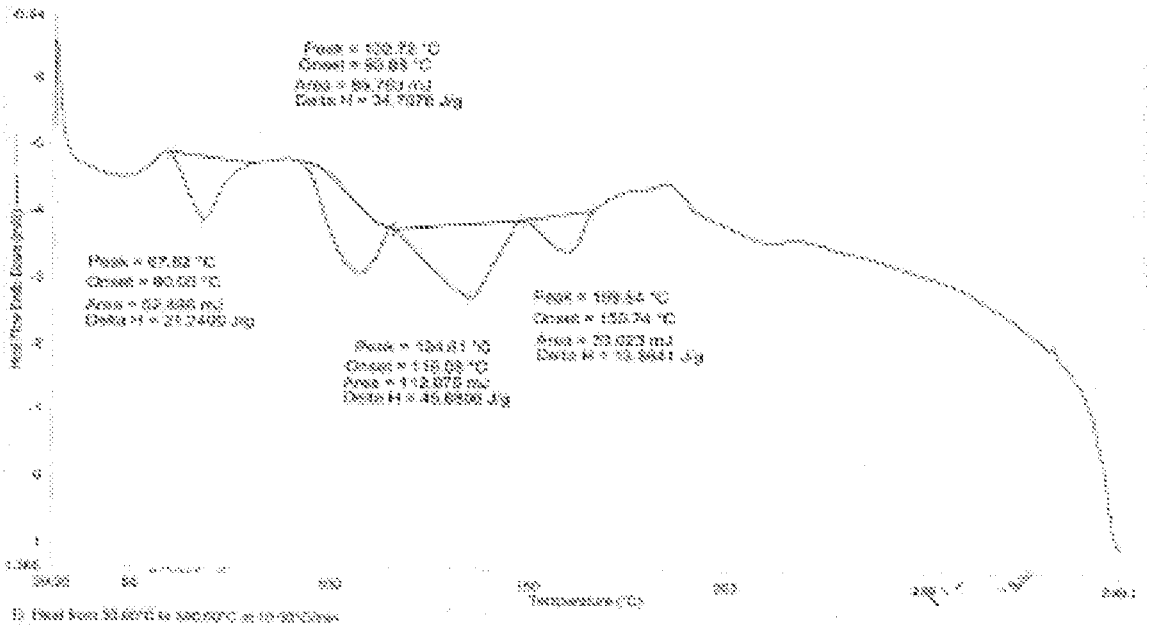


Figure 10: Differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib hydrobromide salt

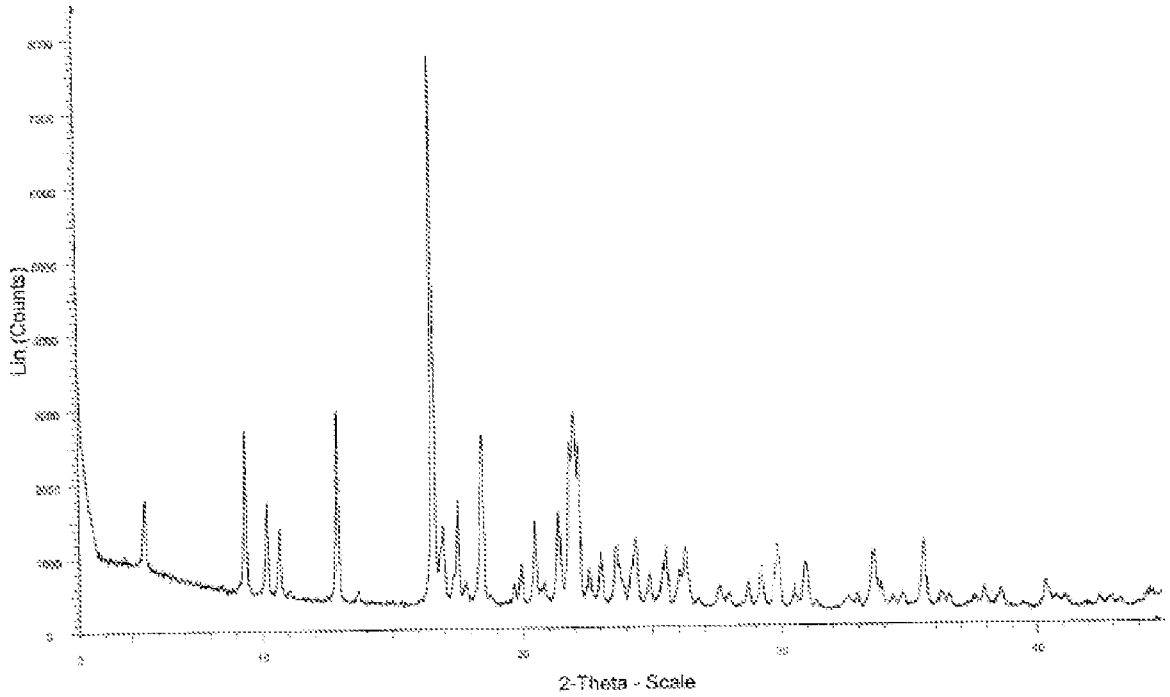


Figure 11: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib glutamate salt

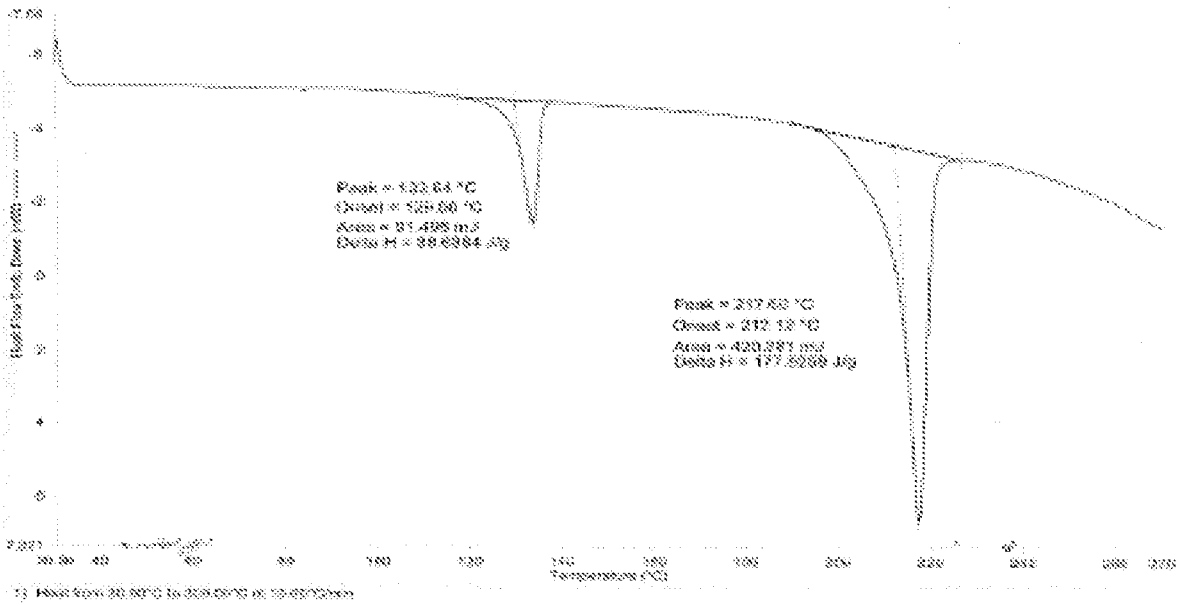


Figure 12: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib glutamate salt

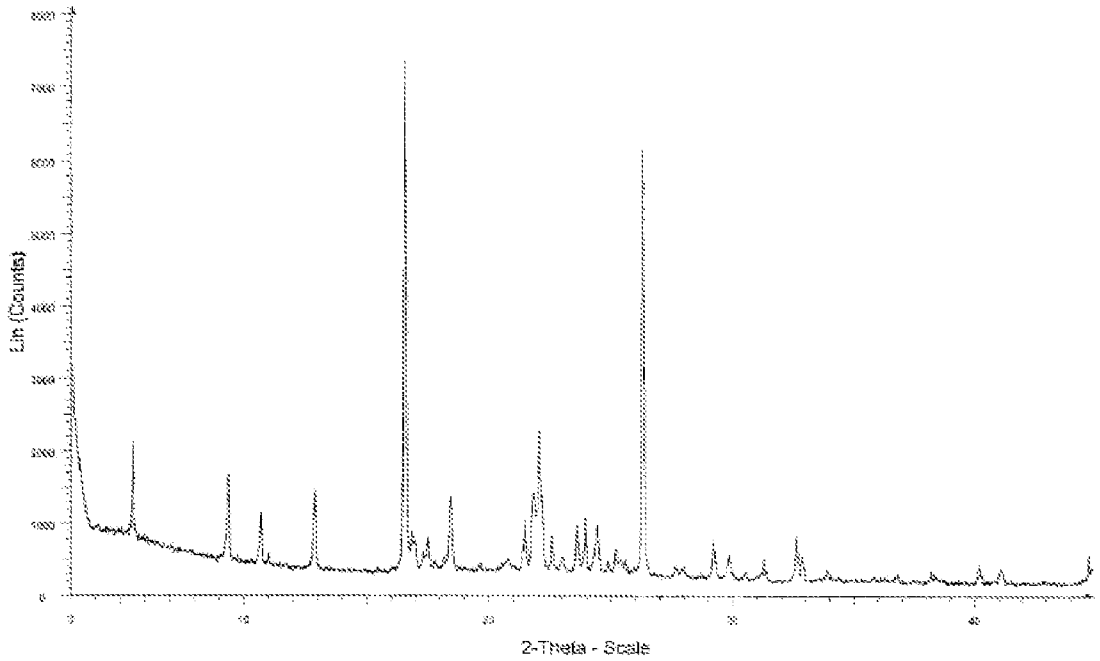


Figure 13: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib sulfamate salt

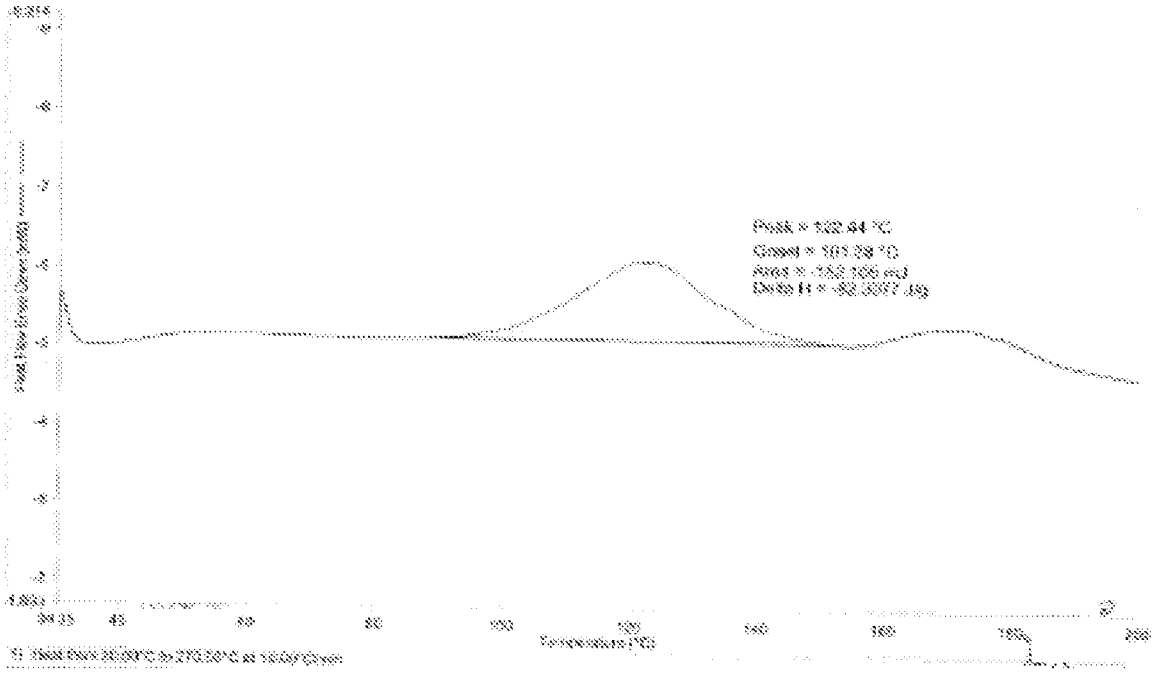


Figure 14: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib sulfamate salt

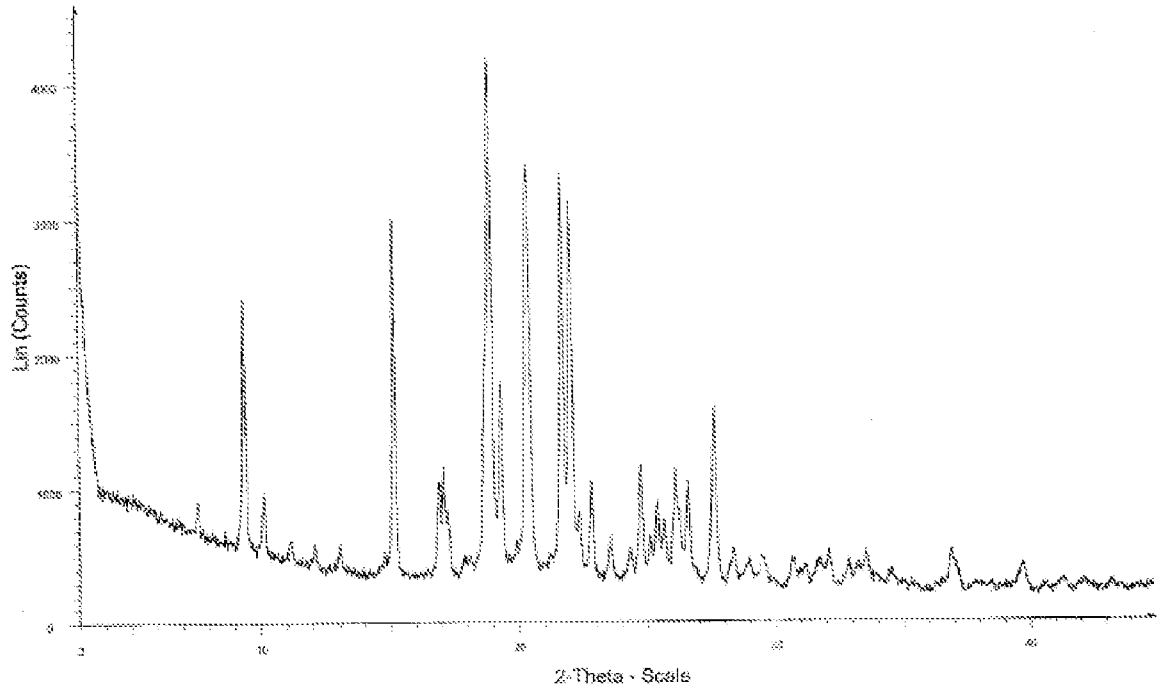


Figure 15: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib benzoate salt

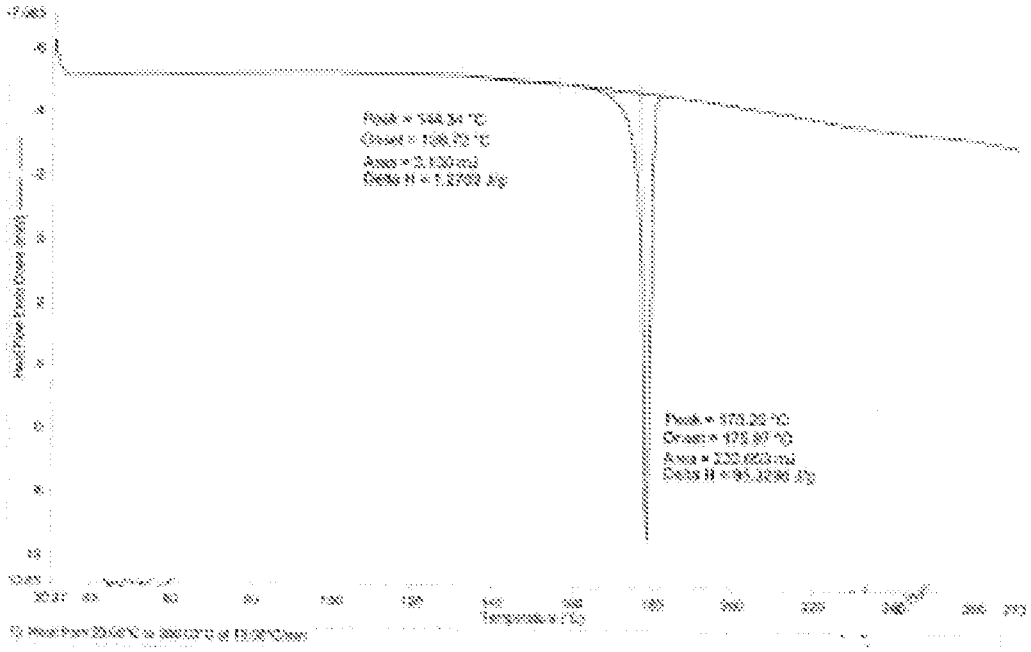


Figure 16: Differential scanning calorimetric (DSC) thermogram of crystalline etoricoxib benzoate salt

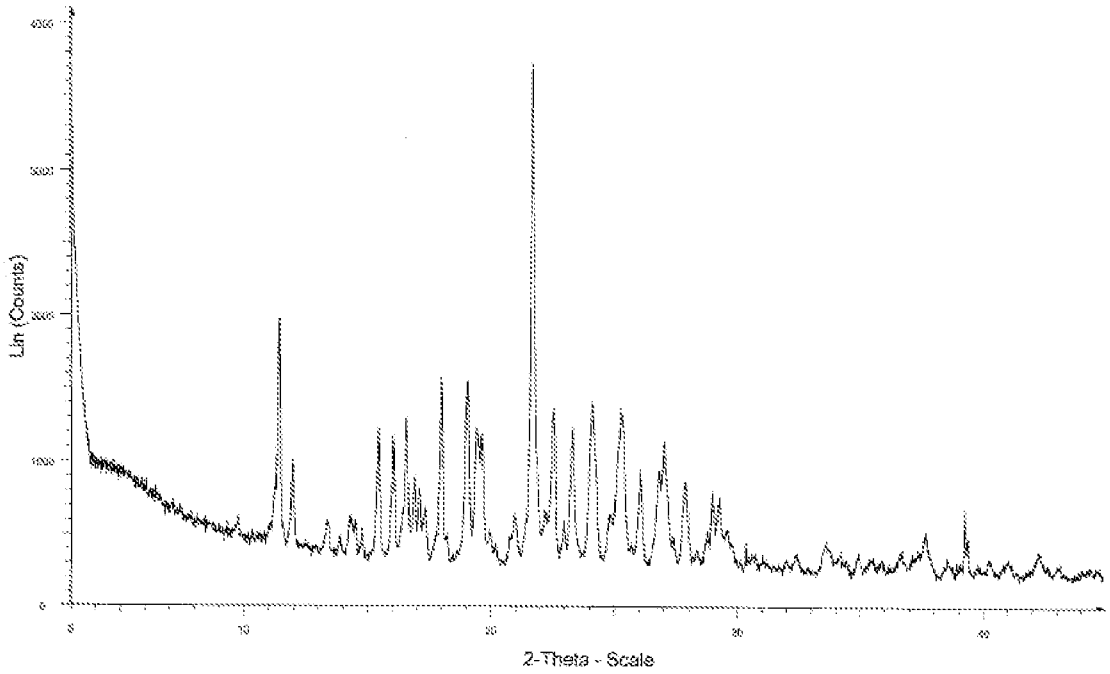


Figure 17: Powder X-ray Diffraction (XRD) pattern of crystalline form I of etoricoxib cinnamate salt

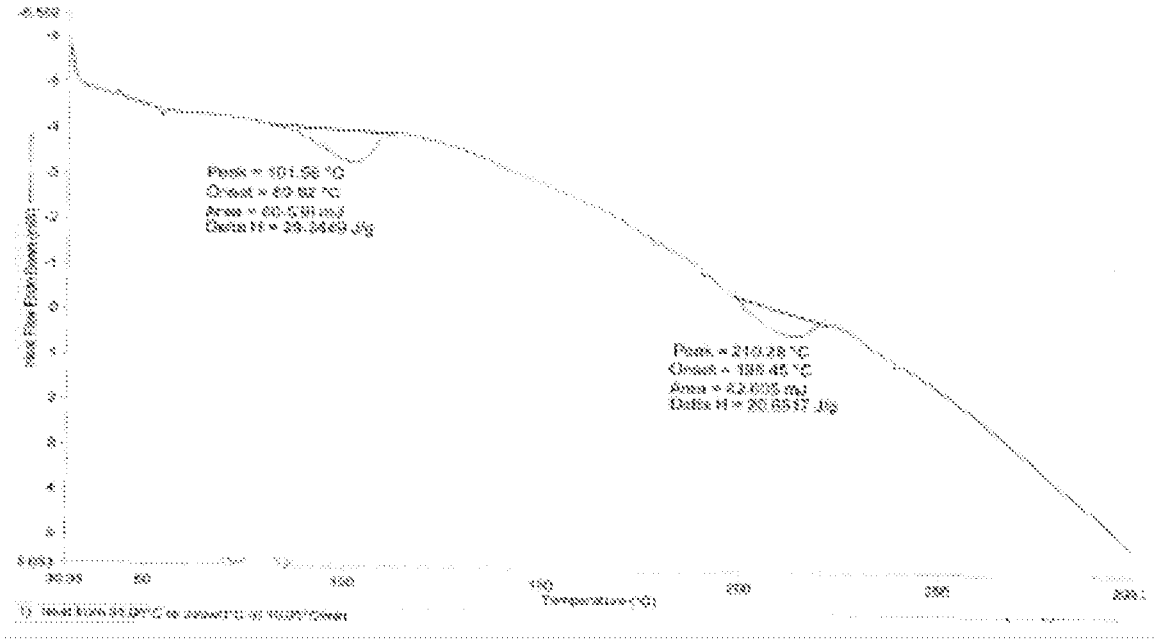


Figure 18: Differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib cinnamate salt

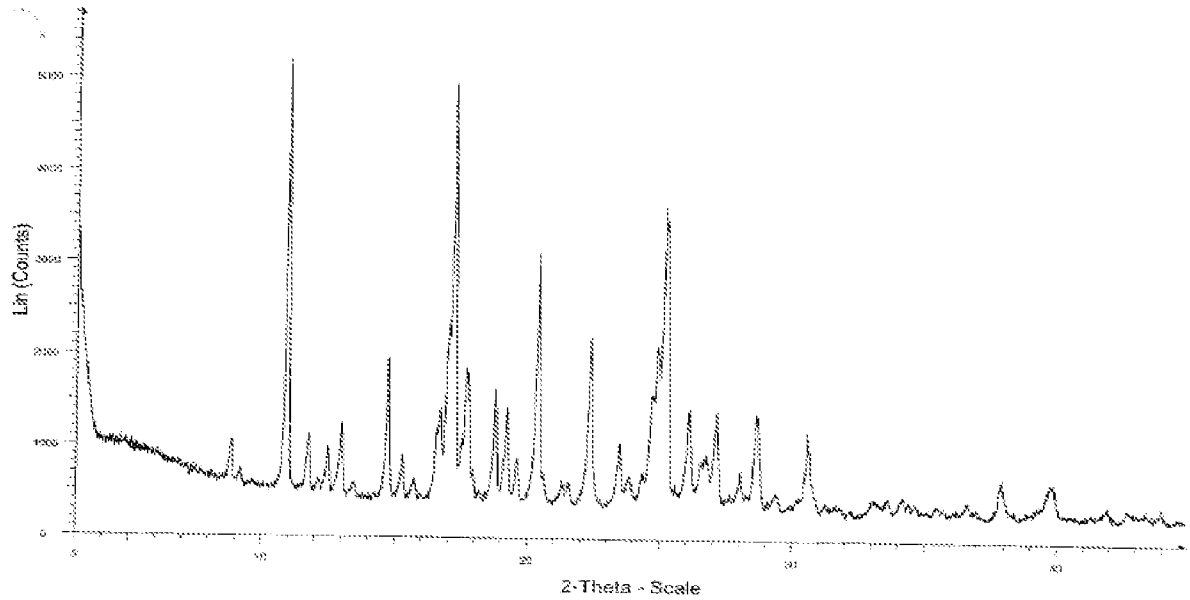


Figure 19: Powder X-ray Diffraction (XRD) pattern of crystalline form II of etoricoxib cinnamate salt

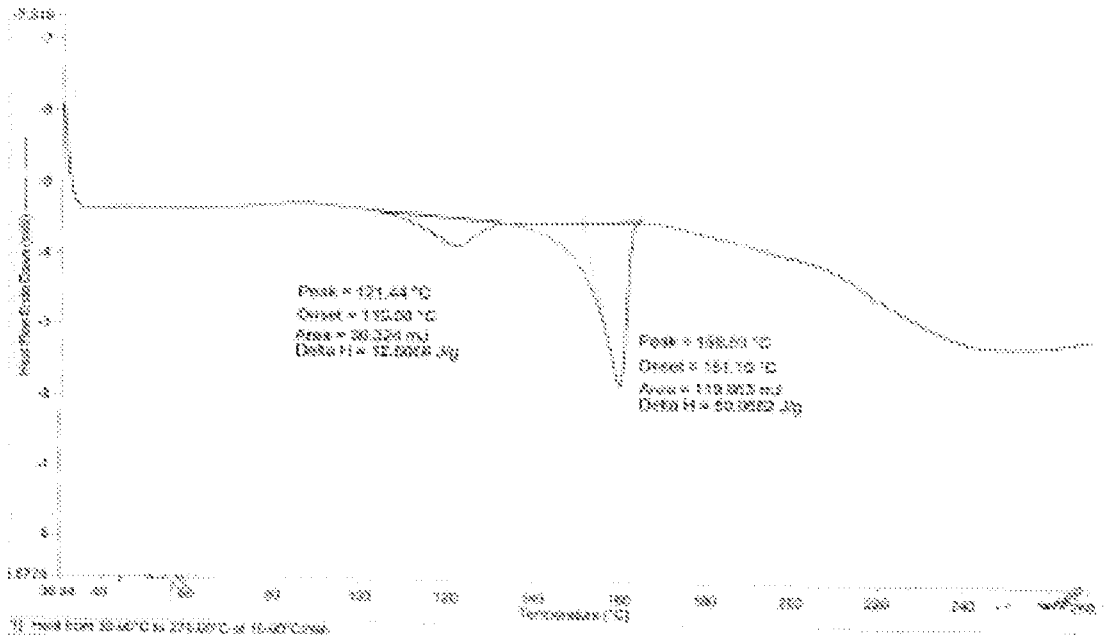


Figure 20: Differential scanning calorimetric (DSC) thermogram of crystalline form II of etoricoxib cinnamate salt

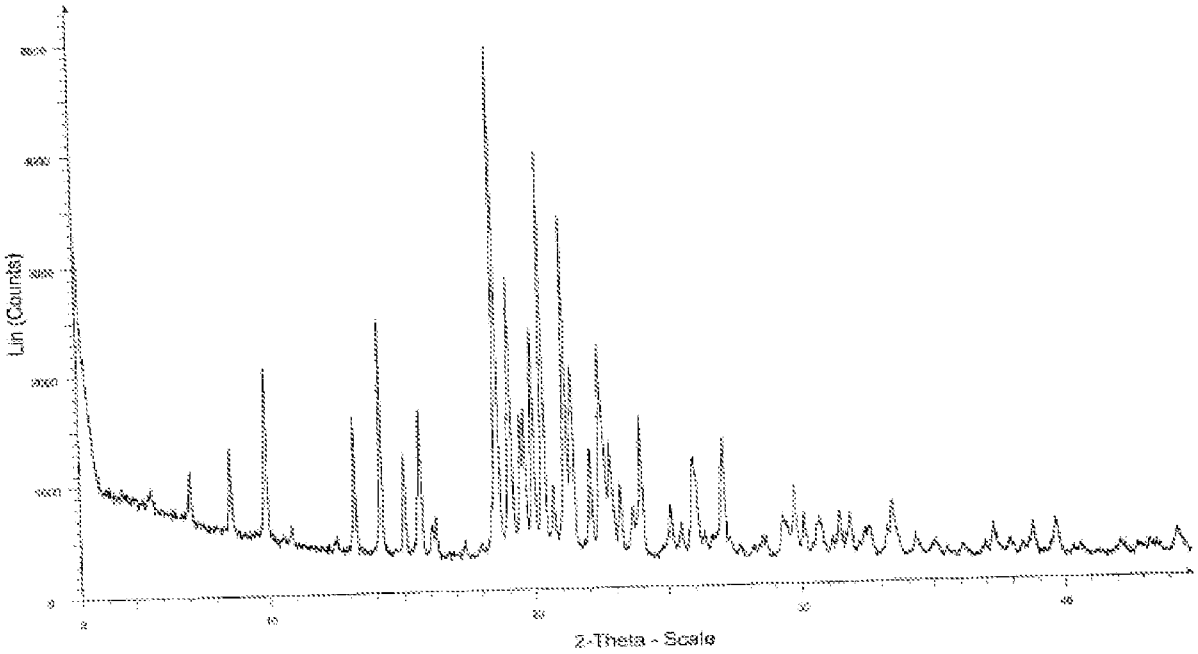


Figure 21: Powder X-ray Diffraction (XRD) pattern of crystalline form I of etoricoxib salicylate salt

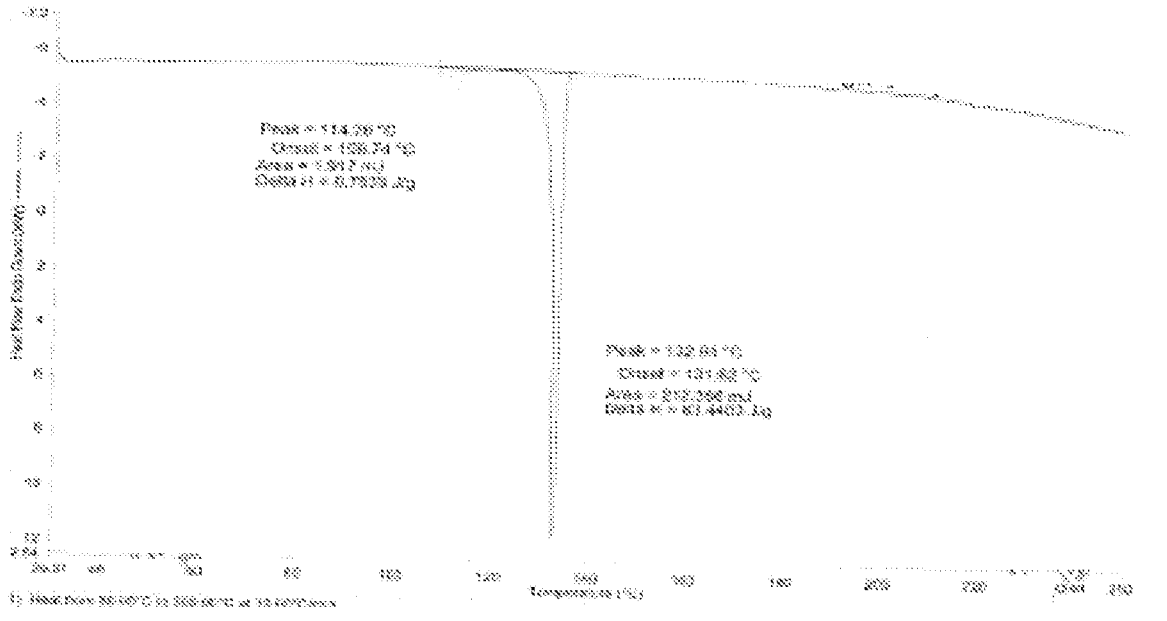


Figure 22: Differential scanning calorimetric (DSC) thermogram of crystalline form I of etoricoxib salicylate salt

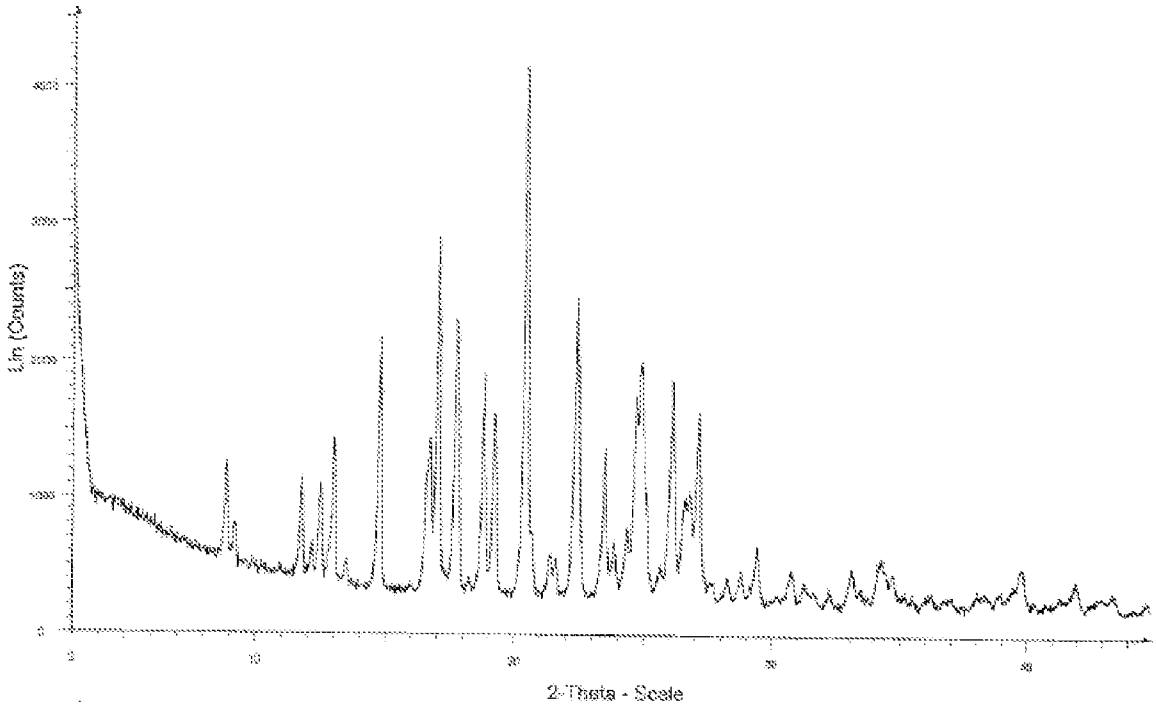


Figure 23: Powder X-ray Diffraction (XRD) pattern of crystalline form II of etoricoxib salicylate salt

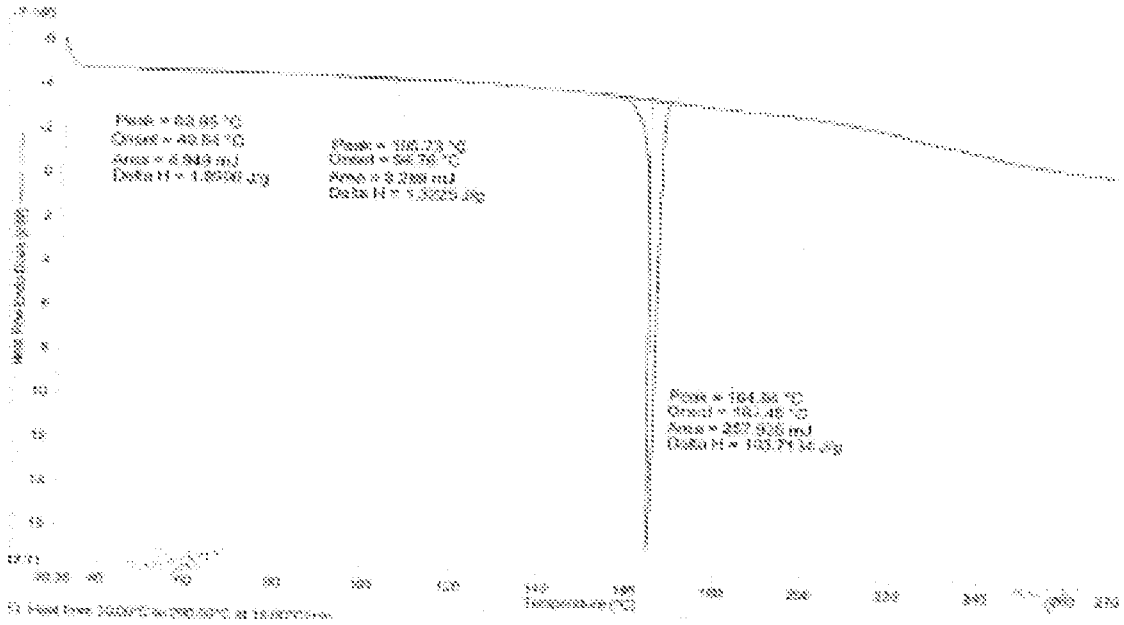


Figure 24: Differential scanning calorimetric (DSC) thermogram of crystalline form II of etoricoxib salicylate salt

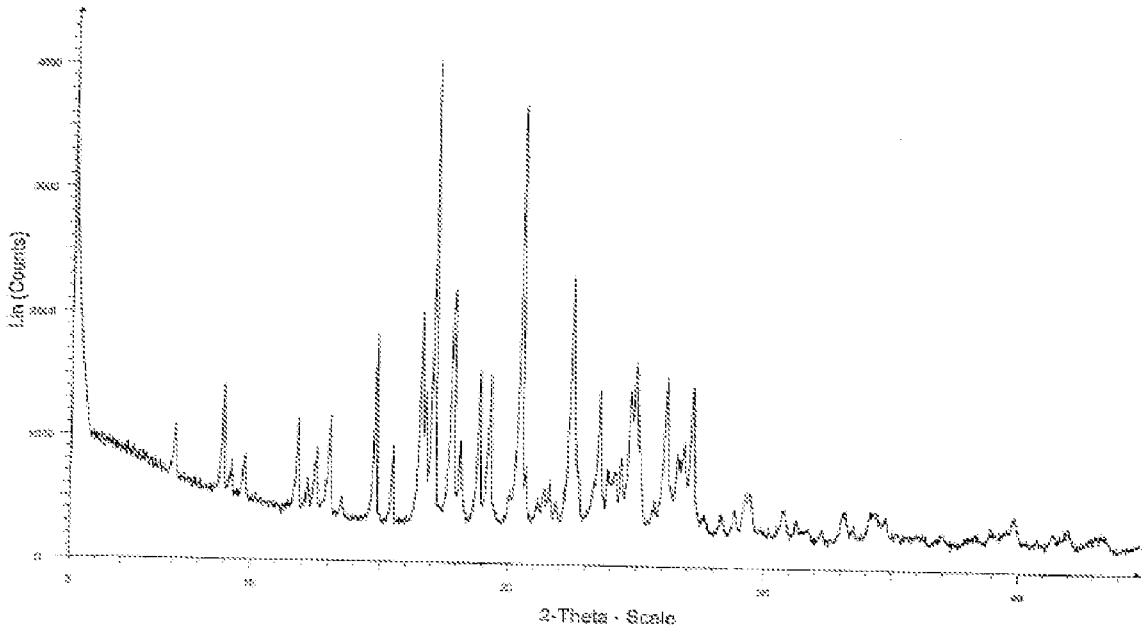


Figure 25: Powder X-ray Diffraction (XRD) pattern of crystalline form III of etoricoxib salicylate salt

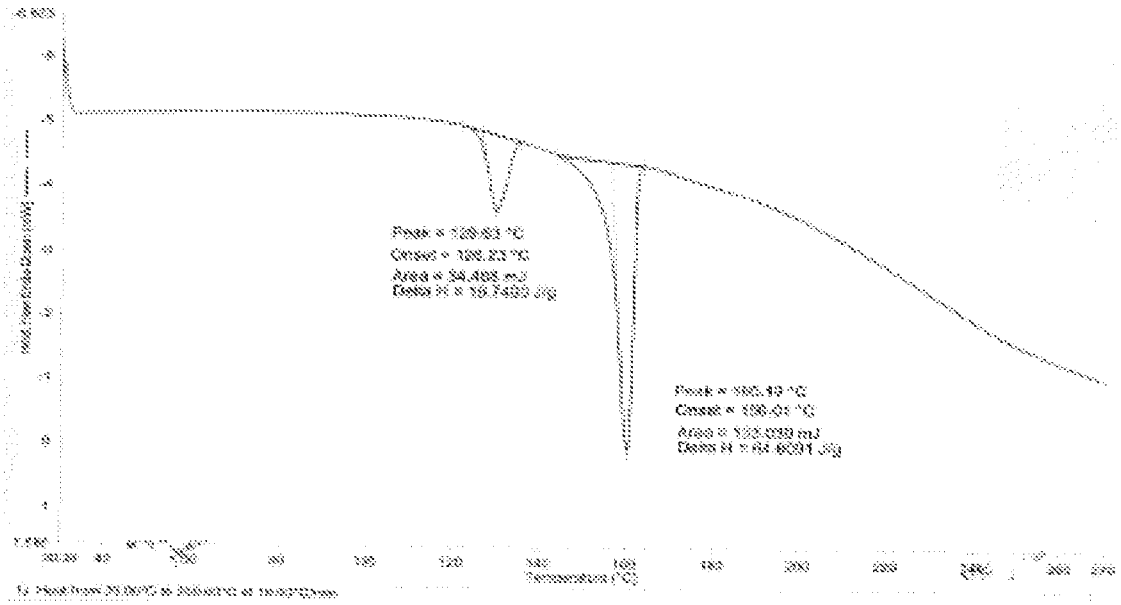


Figure 26: Differential scanning calorimetric (DSC) thermogram of crystalline form III of etoricoxib salicylate salt

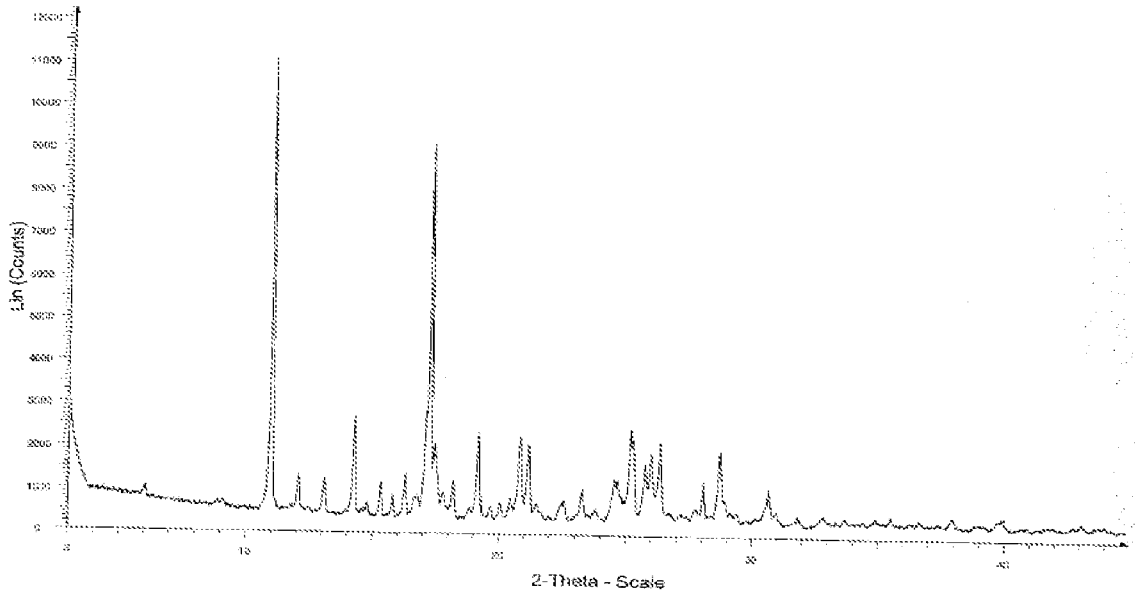


Figure 27: Powder X-ray Diffraction (XRD) pattern of crystalline form IV of etoricoxib salicylate salt

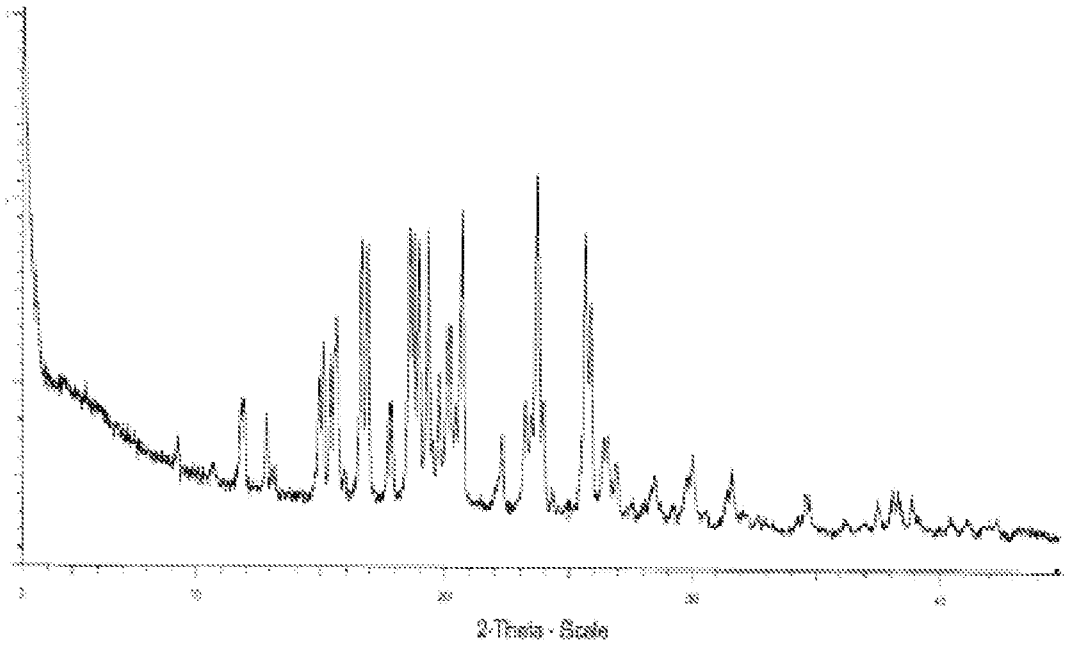


Figure 28: Powder X-ray Diffraction (XRD) pattern of crystalline etoricoxib tosylate salt

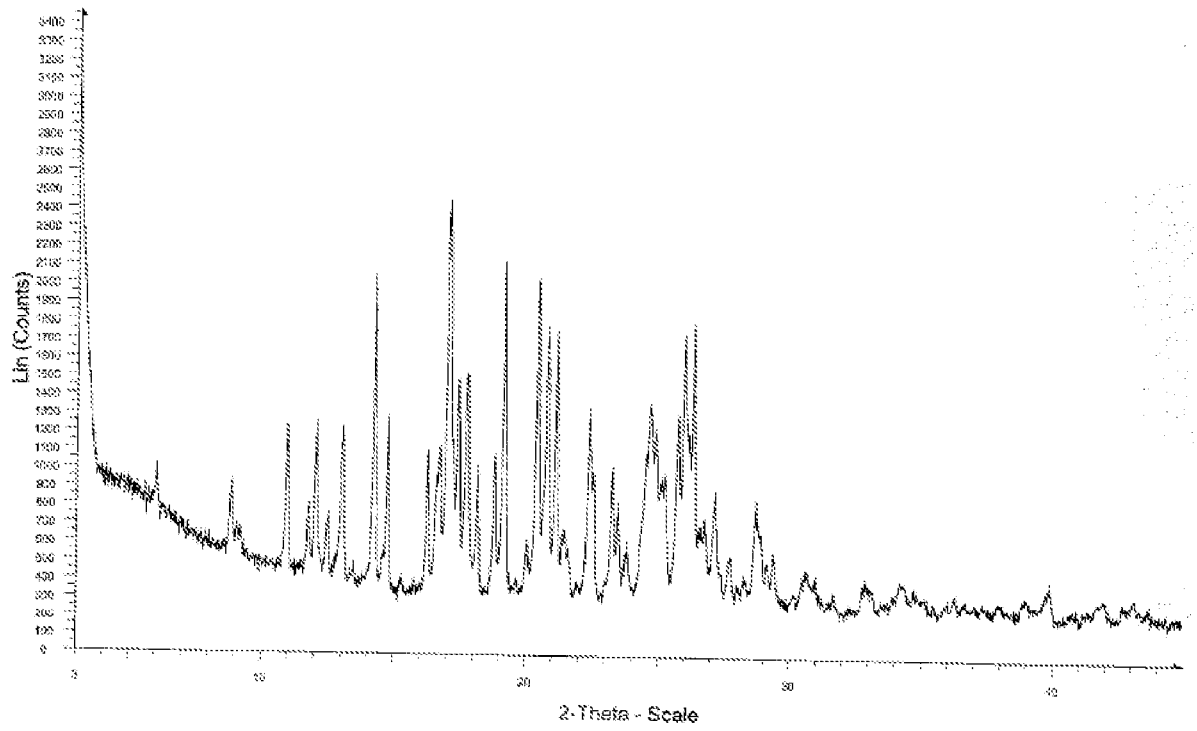


Figure 29: Powder X-ray Diffraction (XRD) pattern of crystalline form II of etoricoxib hydrobromide salt

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/0O2278

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/61 A61K31/444 A61P29/00
ADD.

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 A61K A61P

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 practical, search terms used)

EPO-Internal , EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/03484 A1 (MERCK FROSST CANADA INC [CA] ; DUBE DANIEL [CA] ; FORTIN REJEAN [CA] ; FR) 29 January 1998 (1998-01-29) page 17, line 1 - page 18, line 7; claims 1, 12, 13, 38, 39; example 59; table 1; compound 23	1-17

X	WO 01/92230 A1 (MERCK & CO INC [US] ; CROCKER LOUIS S [US] ; DAVIES IAN W [US] ; OSIFCHIN) 6 December 2001 (2001-12-06) cited in the application page 7, line 14 - page 8, line 16; example H; compound 3	1,2,4,5, 7, 15, 16

☐ 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

"E" earlier document 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
22 November 2011	01/12/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/0O2278

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803484 Al	29-01-1998	AT 249437 T	15-09-2003
		AU 723179 B2	17-08-2000
		BG 64553 Bl	29-07-2005
		CA 2260016 Al	29-01-1998
		CN 1225085 A	04-08-1999
		CO 4900063 Al	27-03-2000
		CY 2409 Bl	10-09-2004
		CZ 9900130 A3	16-06-1999
		DE 69724788 Dl	16-10-2003
		DE 69724788 T2	05-08-2004
		DK 0912518 T3	08-12-2003
		DZ 2268 Al	25-12-2002
		EE 9900018 A	16-08-1999
		EP 0912518 Al	06-05-1999
		ES 2205242 T3	01-05-2004
		HK 1023767 Al	18-03-2005
		HR 970389 A2	30-06-1998
		ID 19602 A	23-07-1998
		IL 127441 A	12-02-2003
		IS 4927 A	18-12-1998
		JP 3251945 B2	28-01-2002
		JP 4246930 B2	02-04-2009
		JP H11514008 A	30-11-1999
		JP 2002080453 A	19-03-2002
		NO 990191 A	16-03-1999
		NZ 333230 A	25-08-2000
		PL 330995 Al	21-06-1999
		PT 912518 E	31-12-2003
		SK 3699 A3	10-12-1999
		TR 9900046 T2	21-04-1999
		WO 9803484 Al	29-01-1998
WO 0192230 Al	06-12-2001	AR 028577 Al	14-05-2003
		AT 483687 T	15-10-2010
		AU 6480401 A	11-12-2001
		AU 2001264804 B2	06-04-2006
		BG 65855 Bl	31-03-2010
		BR 0111140 A	11-01-2005
		CA 2410234 Al	06-12-2001
		CN 1443168 A	17-09-2003
		CR 6606 A	06-02-2006
		CZ 20023888 A3	12-02-2003
		DK 1296951 T3	24-01-2011
		EE 200200655 A	16-08-2004
		EG 24189 A	08-10-2008
		EP 1296951 Al	02-04-2003
		ES 2351958 T3	14-02-2011
		GC 0000362 A	31-03-2007
		HK 1058932 Al	28-07-2006
		HR 20020934 A2	28-02-2005
		HU 0302336 A2	28-11-2003
		IS 6630 A	20-11-2002
		JP 3665053 B2	29-06-2005
		JP 4142621 B2	03-09-2008
		JP 2004501116 A	15-01-2004
		JP 2005047927 A	24-02-2005
		KR 20030003762 A	10-01-2003
		MA 26919 Al	20-12-2004

International application No.
PCT/IB2011/002278

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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 64(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 addi tional 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 oould 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. ☐ 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.:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: Incompletely) ; 1-13, 15-17 (partially)

the oxalate, succinate, fumarate, glutamate, benzoate, cinnamate and salicylate salts of etoricoxib (i.e. derived from a mono- or dicarboxylic acid), the process for preparing them, their use in the process for preparing etoricoxib free base, pharmaceutical compositions containing them and their use in a method of treatment

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2. claims: 1-13, 15-17(all partially)

the besylate, sulfamate and tosylate salts of etoricoxib (i.e. derived from a sulfonic acid), the process for preparing them, their use in the process for preparing etoricoxib free base, pharmaceutical compositions containing them and their use in a method of treatment

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3. claims: 1-13, 15-17 (all partially)

the hydrobromide salt of etoricoxib (i.e. an inorganic salt), the process for preparing them, their use in the process for preparing etoricoxib free base, pharmaceutical compositions containing them and their use in a method of treatment

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/002278

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		MX 230696 B	19-09-2005
		NO 324495 B1	29-10-2007
		NZ 522394 A	28-05-2004
		PA 8516901 A1	25-04-2002
		PE 13242001 A1	28-01-2002
		PL 358153 A1	09-08-2004
		PT 1296951 E	07-12-2010
		RS 51541 B	30-06-2011
		SI 1296951 T1	31-01-2011
		SK 16702002 A3	02-05-2003
		SV 2002000462 A	08-03-2002
		UA 73355 C2	15-04-2003
		WO 0192230 A1	06-12-2001
		ZA 200209558 A	28-10-2003