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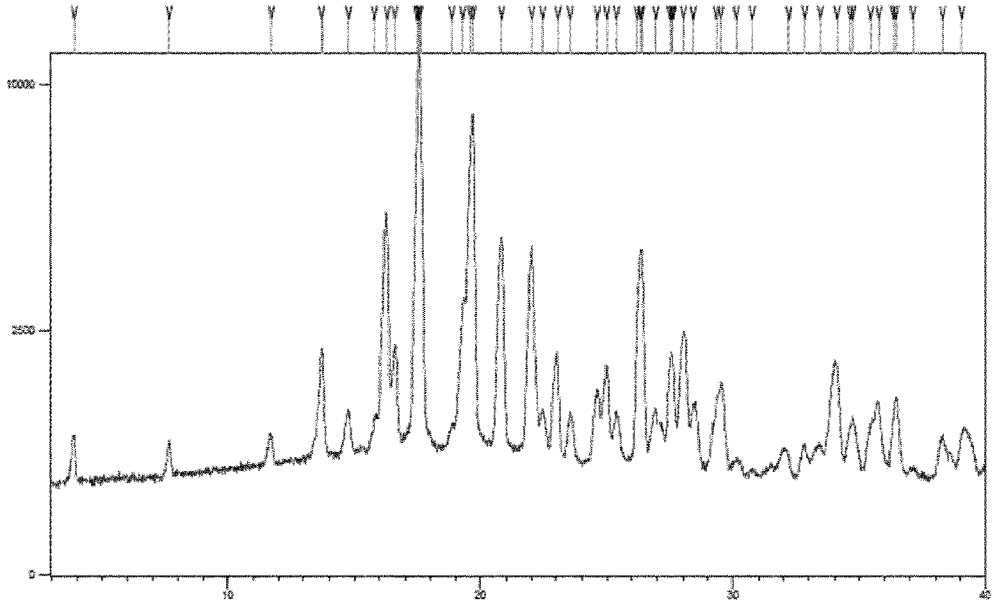
(54) Title: CO-CRYSTAL OF KETOPROFEN, COMPOSITIONS COMPRISING THE SAME, PROCESS OF PRODUCING THE SAME, AND USES THEREOF

Figure 4



(57) **Abstract:** The present invention refers to a co-crystal of Ketoprofen Lysine named Form 1, a pharmaceutical composition comprising said co-crystal, a process for its production and to its use in the treatment of pain and inflammatory diseases.

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TITLE

"CO-CRYSTAL OF KETOPROFEN, COMPOSITIONS COMPRISING THE SAME, PROCESS OF PRODUCING THE SAME, AND USES THEREOF"

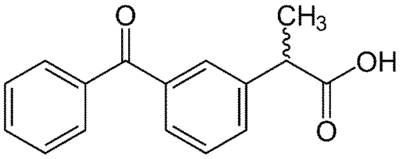
DESCRIPTION

FIELD OF THE INVENTION

The present invention refers to a co-crystal of Ketoprofen Lysine, a pharmaceutical composition comprising said co-crystal, a process for its production and to its medical use, in particular in the treatment of pain and inflammatory diseases.

BACKGROUND OF THE INVENTION

Ketoprofen, ((RS)-2-(3-benzoylphenyl)-propionic acid, chemical formula $C_{16}H_{14}O_3$) of formula



is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID) with analgesic and antipyretic effects.

Because of its high tolerability, Ketoprofen is one of the non-steroidal anti-inflammatory drugs of widespread use in clinics, both for the treatment of serious inflammatory conditions and for its use in analgesic and antipyretic by inhibiting the body's production of prostaglandin.

Pharmaceutical compositions of current use containing Ketoprofen, have a racemate as its active ingredient, where the two enantiomers S(+) and R(-) are present in equimolecular ratio.

The active ingredient is normally used as free acid, practically insoluble in water, in pharmaceutical compositions destined for oral use, while for alternative ways of administration, suitable Ketoprofen Salts with organic and inorganic bases are used. The Salts of Ketoprofen are usefully employed in the treatment of those pathological symptoms of rheumatoid and chronic type, which require the drug to be administered at high dosage, continuously and for long time. It is important and desirable that for the treatment of acute and very painful manifestations, there are pharmaceutical compositions suitable for immediate and manageable use, which rapidly release the active ingredient and are of high bio-availability. Typical examples of these compositions are those by parenteral administration and/or by oral administration, which allow a fine dispersion of the active ingredient.

The solubility and dissolution rate of drugs are decisive factors after oral administration for rate and extent of absorption.

These factors offer a key challenge for the development and formulation of effective drug in the pharmaceutical industry. The issue of poor drugs solubility –which is troublesome for synthesis and development as well- is known and is responsible for bioavailability problems.

Various strategies have been well documented to enhance solubility and dissolution of poorly soluble drugs such as Salt formation, solid dispersion, microemulsion, co-solvency, inclusion complex formation with cyclodextrin etc.

It is also possible to achieve desired properties of a particular active pharmaceutical ingredient (API) by forming a co-crystal of the API itself, or of a Salt of the API. Pharmaceutical co-crystallization has attracted great amount of academic, industrial and therapeutic interests by co-crystallization of two or more pure compounds with crystal engineering to create a new functional material.

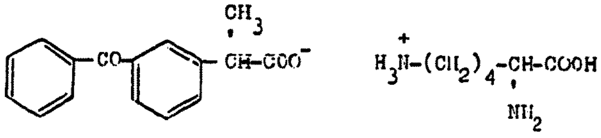
Specifically, pharmaceutical co-crystals are defined as "co-crystals in which the target molecule or ion is an active pharmaceutical ingredient, API, and it bonds to the co-crystal former(s) through hydrogen bonds." (Almarsson M. and Zaworotko J., Chem. Commun., 2004: 1889).

Co-crystals can be also defined as a stoichiometric multi-component system formed between two or more compounds, which are solid under ambient conditions, connected by non-covalent and non-ionic interactions.

Pharmaceutical co-crystals are non-ionic supramolecular complexes and can be used to improve physiochemical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API.

Co-crystals containing API can be used to deliver API therapeutically. New drug formulations comprising co-crystals of API with pharmaceutically acceptable co-formers may, in some cases, have superior properties over existing drug formulations. However, co-crystal formation is not predictable and, in fact, not always possible. Moreover, there is no way to predict the properties of a particular co-crystal of a compound until it is formed. As such, finding the right conditions to obtain a particular co-crystal of a compound, with pharmaceutically acceptable properties, can take significant time, effort, and resources.

The documents GB1497044A and BE882889 describe the preparation of Salts of Ketoprofen with Lysine of formula



through a process in which non-saturated solutions of the components are used.

However, the known Ketoprofen Lysine Salt shows a low crystallinity, possibly associated with undesired water uptake, and rather high particle size, as shown herein in Figure17 and at Table 13. These properties of Ketoprofen Lysine Salt may not be ideal in terms of stability and flowability of the powder or of dissolution profile and bioavailability.

SUMMARY OF THE INVENTION

The Applicant has unexpectedly found that Ketoprofen and Lysine, under certain process conditions, can form a co-crystal (herein named Form 1) which is highly crystalline and characterized by a lower particle size.

An object of the present invention thus refers to a co-crystal of Ketoprofen Lysine (Form 1) characterized by having an X ray diffraction pattern with characteristic peaks at 16.3; 17.5; 17.6; 17.7; 19.6; 19.7° 2theta, with a margin of error on the value indicated for each peak of ± 0.20 degrees (2 theta).

Another object of the present invention is a pharmaceutical composition comprising the co-crystal of Ketoprofen Lysine (Form 1) of the present invention and one or more physiologically acceptable excipients.

Another object of the present invention is a pharmaceutical composition comprising the co-crystal of Ketoprofen Lysine (Form 1) of the present invention in combination with one or more pharmaceutically active agents .

Another object of the present invention refers to the co-crystal of Ketoprofen Lysine (Form 1) and to the pharmaceutical composition comprising said co-crystal for use as a medicament.

Another object of the present invention refers to the co-crystal of Ketoprofen Lysine (Form 1) and to the pharmaceutical composition comprising said co-crystal for the use in the treatment of pain and inflammatory diseases.

Another object of the present invention is a process for the production of the co-crystal of the present invention, wherein said process comprises the following steps:

a) preparing a saturated solution of Ketoprofen;

b) mixing the saturated solution with Lysine;

or

a_1) preparing a saturated solution of Lysine in water;

b_1) mixing the saturated solution with Ketoprofen.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. XRPD of the Ketoprofen-Lysine co-crystal Form 1 collected after evaporation experiment in Dichloromethane.

Figure 2. XRPD of the Ketoprofen-Lysine co-crystal Form 1 collected after precipitation experiments in 1,4-Dioxane (DIX, A), Acetone (ACT, B), Acetonitrile (ACN, C) and N-Methyl Pyrrolidone (NMP, D).

Figure 3. XRPD of the Ketoprofen-Lysine co-crystal Form 1 collected after crystallization experiment in Dichloromethane.

Figure 4. XRPD pattern of Ketoprofen Lysine co-crystal Form 1 obtained with the process of saturated solutions of Lysine (ssLYS) in water.

Figure 5. XRPD pattern of comparative Ketoprofen Lysine Salt obtained according to the process described under Example 2.d.

Figure 6. Comparison between XRPD patterns of Ketoprofen Lysine Co-crystal Form 1 and Ketoprofen Lysine Salt.

Figure 7. NMR Spectra of Ketoprofen Lysine co-crystal Form 1. ^{13}C (100 MHz) CPMAS solid-state NMR spectra acquired at a spinning speed of 12 kHz at room temperature.

Figure 8: 8a. ^{13}C (100 MHz) solid-state CPMAS spectra of comparative Ketoprofen Lysine Salt, acquired at a spinning speed of 12 kHz at room temperature.

8b. ^{13}C (100 MHz) solid-state CPMAS spectra of Ketoprofen Lysine Salt in comparison with Ketoprofen, Lysine and Ketoprofen Lysine Co-crystal Form 1, acquired at a spinning speed of 12 kHz at room temperature.

Figure 9. ^{13}C (100 MHz) CPMAS solid-state NMR spectra in the range 170-210 ppm of samples of racemic Ketoprofen, Ketoprofen Sodium Salt and Ketoprofen Lysine co-crystal Form 1 acquired at a spinning speed of 12 kHz at room temperature. The black dashed line at ca. 177 ppm refers to the chemical shift reported in literature for the protonated carboxylic group of ibuprofen, involved in a H-bond interaction

with a nitrogen atom, in a (ibuprofen)2(4,4'-bipyridyl) co-crystal (Chen S.; Xi H.; Henry R. F.; Marsden I.; Zhang G. G. Z. Cryst Eng Comm 2010, 12, 1485-1493).

Figure 10. FT-IR spectrum of Ketoprofen Lysine co-crystal Form 1.

Figure 11. FT-Raman spectrum of Ketoprofen Lysine co-crystal Form 1.

Figure 12. FT-IR spectrum of comparative Ketoprofen Lysine Salt.

Figure 13. DSC thermogram of Ketoprofen Lysine co-crystal Form 1.

Figure 14. DSC thermogram of Ketoprofen Lysine Salt.

Figure 15. Comparison between the dissolution of Ketoprofen Sodium Salt and Ketoprofen Lysine co-crystal Form 1.

Figure 16. Dissolution rate Ketoprofen Lysine co-crystal Form 1 (formulate).

Figure 17. XRPD pattern of Ketoprofen Lysine co-crystal Form 1 compared with Ketoprofen Lysine Salt.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference; thus, the inclusion of such definitions herein should not be construed to represent a substantial difference over what is generally understood in the art.

The term "physiologically acceptable excipient" herein refers to a substance devoid of any pharmacological effect of its own and which does not produce adverse reactions when administered to a mammal, preferably a human. Physiologically acceptable excipients are well known in the art and are disclosed, for instance in the Handbook of Pharmaceutical Excipients, sixth edition 2009, herein incorporated by reference.

For the purpose of the present invention, the expression "room temperature" means a temperature range of 18-25°C.

For the purpose of the present invention the expression "co-crystal" means a stoichiometric multi-component system, in which the components are connected by non-covalent, non-ionic interactions and, individually, are solid under room conditions.

For the purpose of the present invention, the expression "pain" means pain caused by disturbances of different nature and origin, such as, for example: headache or cephalalgy: both primary and therefore not related to other factors or diseases, and secondary and therefore dependent on trauma, injury and distinct diseases; toothache: in case of abscesses or caries that create pain in the dental pulp, with numerous blood vessels and nerves; menstrual pains: abdominal and lower abdominal pain and headaches caused by hormonal changes typical of the period of menstruation; neuralgia, or intense nerve pain due to strains, trauma and infections; pain in the muscles, or myalgia: pains located at the level of muscles when using or touching them, due to sudden contractions or traumas; osteoarticular pains, such as joint inflammations (to the bones, cartilages, ligaments and tendons) following traumas, old age, strains and injuries.

The terms “approximately” and “about” herein refers to the range of the experimental error, which may occur in a measurement.

The terms “comprising”, “having”, “including” and “containing” are to be construed open-ended terms (i.e. meaning “including, but not limited to”) and are to be considered as providing support also for terms as “consist essentially of”, “consisting essentially of”, “consist of” or “consisting of”.

The terms “consist essentially of”, “consisting essentially of” are to be construed as semi-closed terms, meaning that no other ingredients which materially affects the basic and novel characteristics of the invention are included (optional excipients may thus be included).

The terms “consists of”, “consisting of” are to be construed as closed terms.

The term “saturated solution” is to be construed as a chemical solution containing the maximum concentration of a solute dissolved in the solvent at a certain temperature. In the present context, if not otherwise stated, reference is made to room temperature.

A first object of the present invention refers to a co-crystal of Ketoprofen Lysine (Form 1) characterized by having an X ray diffraction pattern (XRPD) with characteristic peaks at 16.3; 17.5; 17.6; 17.7; 19.6; 19.7° 2theta, with a margin of error on the value indicated for each peak of ± 0.20 degrees (2 theta).

The typical XRPD pattern of said co-crystal is represented in Figure 4.

As reported in Table 4, the XRPD diffractogram shows relevant signals in the region from 17 to 25° 2theta.

In particular, Ketoprofen Lysine co-crystal Form 1 shows the most characterizing peaks at 16.2898; 17.4718, 17.5514; 17.6104; 17.6712; 19.5987; 19.7109° 2theta.

In addition, the co-crystalline nature of Ketoprofen Lysine Form 1 of the present invention is shown in the ^{13}C ss-NMR (solid state NMR) spectra, so as depicted in Figure 7 and Table 6A.

Preferably, the molecular ratio between Ketoprofen and Lysine of the co-crystal of the present invention is 1:1.

In order to determine said molecular ratio two software packages were used for the structure determination from powder diffraction data: Biovia Material Studio Reflex and EXPO2014, so as reported in the experimental section. These methodologies can be adopted for solving crystal structure by X-ray powder diffraction data. The collected powder is crystalline and the pattern was indexed with a monoclinic cell. Four Ketoprofen and four Lysine molecules were identified in the cell (1:1 stoichiometric ratio).

Preferably, the co-crystal of the present invention is co-crystal of (R)-2-(3-benzoylphenyl)-propionic acid D-Lysine.

Preferably, the co-crystal of the present invention is co-crystal of (R)-2-(3-benzoylphenyl)-propionic acid L-Lysine.

Preferably, the co-crystal of the present invention is co-crystal of (S)-2-(3-benzoylphenyl)-propionic acid D-Lysine.

Preferably, the co-crystal of the present invention is co-crystal of (S)-2-(3-benzoylphenyl)-propionic acid L-Lysine.

The co-crystal of Ketoprofen Lysine (Form 1) of the present invention differs from Ketoprofen Lysine Salt as shown in the XRPD comparison of Figure 6, in the ^{13}C CPMAS solid-state NMR comparison of Figure 8b and in FT-IR comparison of Figures 10 and 12.

Advantageously, the co-crystal of Ketoprofen Lysine of the present invention shows a high dissolution rate, so as reported in Figure 15.

Thus, the high dissolution rate of the co-crystal of Ketoprofen Lysine Form 1 of the present invention allows its use in the treatment of those pathological and chronic symptoms, which require the drug to be administered at high dosage, continuously and for long period of time.

Furthermore, the co-crystal of Ketoprofen Lysine Form 1 of the present invention shows lower particle size, as reported in Table 13, and greater crystallinity than previous Ketoprofen Lysine Salt, as shown in Figure 17.

Preferably, the co-crystal Form 1 according to the present invention has a particle size distribution with a D90 lower than 300 µm, preferably lower than 250 µm, more preferably lower than 200 µm.

Preferably, the co-crystal Form 1 according to the present invention has a particle size distribution with a D90 from 100 µm to 300 µm, preferably from 150 to 250 µm, more preferably 170 µm to 200 µm.

These properties are advantageous in the setting of the fluid-dynamic process parameters during the production of the coated granulate of Ketoprofen Lysine. The evaluation of the dynamic flow and the shear properties as well as stability of the powder through tests such as basic stability energy, stability index, specific energy and conditioned bulk density shows greater friction phenomena in the powder bed for Ketoprofen Lysine Salt compared to Co-crystal. The phenomenon could be derived from the greater amorphous degree, the irregular shape and the higher hygroscopicity of the Ketoprofen Lysine Salt compared to the present Co-crystal.

Another object of the present invention refers to pharmaceutical compositions comprising the co-crystal of Ketoprofen Lysine Form 1 of the present invention.

The pharmaceutical composition of the present invention is suitable for immediate and manageable use, and rapidly releases the API.

Preferably, the pharmaceutical composition of the present invention further comprises physiologically acceptable excipients.

More preferably, said excipients are selected from the group consisting of: povidone, colloidal silica, hydroxypropylmethylcellulose, eudragit EPO, sodium dodecyl sulfate, stearic acid, magnesium stearate, aspartame, mannitol, xylitol, talc, flavors.

Preferably, the pharmaceutical composition of the present invention is in a solid form, more preferably in solid granulate form.

As reported in Figure 16, the solid granulate form of the co-crystal of Ketoprofen Lysine Form 1 shows high dissolution rate.

Another object of the present invention is the co-crystal of Ketoprofen Lysine Form 1 and the pharmaceutical composition comprising said co-crystal for medical use, preferably for use in the treatment of pain and inflammation diseases.

Preferably, the co-crystal of Ketoprofen Lysine Form 1 and the pharmaceutical composition comprising said co-crystal are used in the treatment of pain, in which the pain is selected from the group consisting of: acute pain, headache, toothache, menstrual pain, muscle pain, osteoarticular pain.

Preferably, the co-crystal of Ketoprofen Lysine Form 1 and the pharmaceutical composition comprising said co-crystal are used in the treatment of inflammation diseases, in which the inflammation diseases are selected from the group consisting of rheumatic diseases.

Advantageously, the co-crystal of the present invention can be obtained by starting from a saturated solution.

Another object of the present invention is a pharmaceutical composition comprising the co-crystal of Ketoprofen Lysine (Form 1) of the present invention in combination with one or more pharmaceutically active agents.

Another object of the present invention is a process for the production of the co-crystal of the present invention, wherein said process comprises the following steps:

a) preparing a saturated solution of Ketoprofen;
b) mixing the saturated solution with Lysine;

or

a_1) preparing a saturated solution of Lysine in water;
b_1) mixing the saturated solution with Ketoprofen.

Advantageously, with the process of the present invention a significantly high yield is obtained, so as reported in Table 3A.Preferably, the equivalent ratio between saturated Ketoprofen and Lysine or between saturated Lysine and Ketoprofen is 3:1 or higher.

Preferably, in the process comprising the steps a) and b) (process 2.c.i in the experimental part), the equivalent ratio between Ketoprofen in the saturated solution and Lysine is from 10:1 to 1:1, more preferably from 3:1 to 1:1.

Preferably, in the process comprising the steps a) and b), the ratio between the amount of Lysine by weight (mg) and the volume (ml) of the saturated solution of Ketoprofen is comprised between 1 mg/ml and 90 mg/ml, preferably from 4 mg/ml to 70 mg/ml, more preferably from 5 mg/ml to 60 mg/ml.

Preferably, the solvent used for the saturated solution of Ketoprofen is selected form the group consisting of: alcohols, ethers, esters, amides, ketones, aromatic solvents, halogenated solvents and aprotic dipolar solvents.

More preferably, said alcohols are selected from the group consisting of: ethanol, methanol, 1-butanol, 1-propanol, 2-butanol, 2-propanol, 1-pentanol and benzyl alcohol.

More preferably, said ethers are selected from the group consisting of: 1,4-dioxane and tetrahydrofuran.

More preferably, said esters are selected from the group consisting of: ethyl acetate, methyl acetate, propyl acetate.

More preferably, said amides are selected from the group consisting of: N,N, dimethylacetamide and 1-methyl-2-pirrolidone.

More preferably, said ketones are selected from the group consisting of: acetone, cyclopentanone, 4-Methyl-2-Pentanone.

More preferably, said aromatic solvents are selected from the group consisting of: toluene, benzonitrile, p-xylene.

More preferably, said halogenated solvents are selected from the group consisting of: dichloromethane,1,2-dichloroethane and chloroform.

More preferably, said aprotic dipolar solvents are selected from the group consisting of:

dimethylsulphoxide, acetonitrile.

Admixtures of two or more of the above solvents can be used as well.

Preferably, said mixing step b) or b_1) is carried out at a temperature from 5°C to 30°C, more preferably at room temperature.

Preferably, said mixing step b) or b1) is carried out, preferably by stirring, at a temperature from 15°C to 30°C, for 10 to 72 hours, more preferably by stirring at room temperature for 24 hours.

The co-crystal of the present invention can be also obtained by evaporation (process 2.a of the present experimental part). Said process comprises the step of:

a’) mixing Ketoprofen and Lysine in a halogenated solvent up to provide a solution, wherein said Ketoprofen is in stoichiometric excess in comparison to Lysine;

b’) evaporating the solution obtained from step a’) to provide a solid, and

c’) optionally slurrying the solid in a solvent.

Preferably, the equivalent ratio between Ketoprofen and Lysine of step a’) is 8:1 or higher.

Preferably, said halogenated solvent is selected from the group consisting of: dichloromethane, chloroform, 1,2-dichloroethane. More preferably, said solvent is dichloromethane.

Preferably, said mixing is carried out by stirring for 1 hour at room temperature.

Preferably, said evaporating of step b') is carried out at room temperature.

Preferably, the solution of step a') is filtered before step b').

Preferably, the slurrying of step c') is carried out in a solvent selected from isopropyl ether, 2-Methyl-1-Propanol, Methyl Ethyl Ketone.

Advantageously, with said alternative process a high yield is obtained by using dichloromethane as the halogenated solvent, so as reported in Table 1.

The co-crystal of the present invention can be also obtained by a process involving a precipitation technique (process 2.b of the experimental part). Said process comprises the following steps:

a'') mixing an aqueous solution of Lysine with a Ketoprofen solution,

b'') adding the solvent of the Ketoprofen solution until a solid is formed.

Preferably, said process comprises the following steps:

a'') mixing an aqueous solution of Lysine with a non-aqueous Ketoprofen solution in a non-aqueous solvent, to provide an admixture,

b'') adding the non-aqueous solvent of the Ketoprofen solution to the admixture until a solid is formed.

With the term "non-aqueous solution" a solution comprising less than 10%, preferably, less than 5%, more preferably less than 1%, even more preferably less than 0.5% or 0.1 % ww of water is meant.

Preferably, the Ketoprofen and Lysine of step a'') are in 1:1 equivalents ratio.

Preferably, the non-aqueous solvent of said Ketoprofen non-aqueous solution is selected from the group consisting of alcohols, ethers, amides and ketones, as above listed.

Preferably, said steps a'') and b'') are carried out at room temperature. The co-crystal of the present invention can be also obtained by a process involving another precipitation technique (process 2.c.ii of the experimental part). Said process comprises the following steps:

a''') preparing a non-saturated solution of Ketoprofen in a solvent selected from the group consisting of Acetone, Chloroform, Cyclopentanone, 1,4-Dioxane, DMSO, Ethanol, Methanol, 1-Methyl-2-Pyrrolidone and Tetrahydrofuran;

b''') mixing the non-saturated solution of Ketoprofen with Lysine, wherein the equivalent ratio between Ketoprofen and Lysine is 3:1.

As can be seen in the experimental part (Table 3B), a variation in the equivalent ratio between Ketoprofen and Lysine does not provide the desired product.

Preferably, the non-saturated solution of step a''') has a concentration of Ketoprofen from 400 mg/ml to 250 mg/ml, more preferably from 350 mg/ml to 250 mg/ml.

EXPERIMENTAL PART

In the following, some non-limitative examples are provided related to the computational calculation and production process of the co-crystal of Ketoprofen Lysine Form 1, its yields, XRPD analysis, NMR analyses, FT-IR analysis, RAMAN analysis, dissolution rate and particle size distribution.

Furthermore, comparative examples with Ketoprofen Sodium Salt and Ketoprofen Lysine Salt, their analytical characterization and their comparison of properties are provided.

1. COMPUTATIONAL STUDY

Two software packages were used for the structure determination from powder diffraction data:

- Biovia Material Studio Reflex; and
- EXPO2014.

These methodologies can be adopted for solving crystal structure by X-ray powder diffraction data. Four Ketoprofen and four Lysine molecules were identified in the cell (calculated volume 2111 Å^3).

The space group was assigned checking the systematic absences in the first part of the pattern. The reflections 0 0 l (l=2n+1), 0 k 0 (k= 2n+1) and h 0 l (l= 2n+1) have zero intensity which suggest the space group $P2_1/_c$ with only one couple Ketoprofen-Lysine forming the asymmetric unit.

Starting from a high-quality powder containing of Ketoprofen Lysine, a correct solution has been achieved with an enough correlation between experimental powder pattern and the simulated one. Material Studio Reflex (1) available from BIOVIA and EXPO2014 (2) software, has been applied.

Biovia Material Studio Reflex allows to indexing the experimental powder by using accurate methods: TREOR90 (3), DICVOL91 (4), and ITO (5), determining the cell parameters and crystal system. After that, the Pawley (6) refinement helps to refines the cell parameters, peak shape, and background values. Some specific settings such us weighted R-factor and R_{wp} (weighted profile R-factor) are optimized in order to get agreement between the experimental and simulated powder diffraction pattern. The next step involves the powder solving. Material Studio Reflex go through an indirect method that employs a Monte Carlo simulated annealing or parallel tempering algorithms. This obtained simulated pattern is then compared to the experimental powder pattern using R_{wp} as a measure of similarity. Structures with low R_{wp} values are automatically saved to trajectory files. Multiple cycles to determine the structure are performed to confirm the final solution. A final refinement of the proposed solution is performed with the rigid-body Rietveld (7; 8) refinement. EXPO2014 allow to obtain the crystal structure solution via “Direct Methods” and/or by a direct-space approach, and the structure refinement by the Rietveld technique. The first step includes the indexing process carried out with program N-TREOR09 (9), followed by space-group determination analysis. To solve the correct solution, we used a specific direct-space technique, such as simulated annealing (SA), ensuring to directly accommodate the structure model by using the fitting between the experimental and calculated profile. The SA approach tries to solve crystal structures by moving a molecular model in the monoclinic cell, adjusting its orientation until the minimum of a suitable cost function, is reached. The last step in the ab initio crystal structure solution is the completion and refinement of the structure model. In the case of powder data the Rietveld (7) method is the most popular technique.

2. PRODUCTION PROCESSES

2.a EVAPORATION

The experiments were performed preparing a clear solution of racemic Lysine and racemic Ketoprofen.

In order to prepare the solution, 29 mg of Lysine and 50 mg of Ketoprofen were weighed in a 8 mL vial and 5 mL of Dichloromethane was added.

Since Lysine was not soluble in these conditions, Ketoprofen was added portion-wise to promote Lysine dissolution.

Eight equivalents of Ketoprofen were added and the solution of Lysine (1 equivalent) in dichloromethane, stirred for 1 hour at room temperature, filtered and left to evaporate at 25°C.

A sticky solid was recovered after the experiment, so it was further slurried in 2 mL of Isopropyl Ether (IPE) for 48 hours.

After this time, a white solid was isolated with a yield of 90% and analyzed by XRPD. The presence of Ketoprofen-Lysine co-crystal Form 1 was observed, as reported in Figure 1.

The same evaporation experiment, has been carried out in the same conditions, but using chloroform and 1,2-dichloroethane instead of dichloromethane. As reported in the Table 1, the yield is better by using dichloromethane.

Table 1.

Results of evaporation tests

Solvent	KET eq.	T (°C)	Aspect after Evaporation	XRPD	Yield (%)
Dichloromethane	8	25	Sticky solid, slurry in IPE	KET-LYS	90
Chloroform	8	25	Sticky solid, slurry in IPE	KET-LYS	68
1,2-Dichloroethane	8	25	Sticky solid, slurry in IPE	KET-LYS	60

2.b PRECIPITATION

Precipitation experiments were performed by preparing a solution of Lysine in water and solutions of Ketoprofen in selected solvents (see Table 2), then adding dropwise these to aqueous solution of racemic Lysine. 29 mg of Lysine (0.198 mmol) were dissolved in 0.1 mL of water, while 50 mg (0.198 mmol, 1 eq.) of Ketoprofen was dissolved in 0.5 mL of the selected solvent (see Table 2), also used as anti-solvent for the precipitation.

After the addition of Ketoprofen, the solution was stirred for 15 minutes, and if no precipitation was observed, more solvent was added dropwise until the formation of a solid.

After this time, a white solid was isolated and analyzed by XRPD. The presence of Ketoprofen-Lysine co-crystal Form 1 was observed, as reported in the following Table 2 and Figure 2.

Table 2.

Results of precipitation experiments Stoichiometric Ratio Ketoprofen : Lysine 1:1

Solvent	mL of solvent added	XRPD	Yield (%)

1-Butanol	1	KET-LYS	72
1-Pentanol	2	KET-LYS	60
1-Propanol	1	KET-LYS	68
(±) 2-Butanol	1	KET-LYS	66
2-Propanol	1	KET-LYS	60
Acetonitrile	1	KET-LYS	65
Acetone	1	KET-LYS	63
1,4-Dioxane	1	KET-LYS	52
N,N-Dimethylacetamide	1	KET-LYS	58
N,N-Dimethylformamide	1	KET-LYS	55
1,2-Dimetoxy Ethane	1	KET-LYS	50
Ethanol	1	KET-LYS	78
Methanol	3	KET-LYS	68
2-Methyl Propanol	1	KET-LYS	70
N-Methyl-2-Pyrrolidone	1	KET-LYS	56
Tetrahydrofuran	3	KET-LYS	54

2.c.i CRYSTALLIZATION FROM KETOPROFEN SATURATED SOLUTION

The experiments were performed by adding a saturated solution of Ketoprofen to 29 mg of racemic Lysine. Saturated solutions were prepared by dissolving 50 mg of Ketoprofen in the selected solvent (see Table 3) in an 8 mL glass vial equipped with a magnetic stirring bar at room temperature.

The solution was stirred until complete dissolution of the solid. More Ketoprofen was then manually added to the solution until no further Ketoprofen dissolved.

The solution was left to equilibrate for approx. 4 hours and the final solution was withdrawn from the vial using a plastic syringe and filtered using a 0.45 µm syringe filter to remove any excess solid.

The filtered solution was then added to racemic Lysine (29 mg, 0.198 mmol) and the resulting mixture was stirred at room temperature for 24 hours.

After this time, a small amount of the formed solid was recovered and analyzed by XRPD. When no solid was recovered, the solution was left to evaporate until the formation of a solid was observed.

The results observed after these experiments are reported in the Table 3A.

Table 3A.

Results of crystallization experiments from Ketoprofen saturated solution

Solvent	Volume of ssKET (mL)	XRPD	Yield
1-Butanol	0.5	KET-LYS	70
1-Pentanol	0.5	KET-LYS	62
1-Propanol	0.5	KET-LYS	67
(±) 2-Butanol	0.5	KET-LYS	62
2-Propanol	0.5	KET-LYS	67
Benzyl Alcohol	0.5	KET-LYS	80
Benzonitrile	0.5	KET-LYS	68
Dichloromethane	0.5	KET-LYS	88
N,N-Dimethylacetamide	0.5	KET-LYS	53
Ethyl Acetate	0.5	KET-LYS	75
Methyl Acetate	0.5	KET-LYS	72
4-Methyl-2-Pentanone	0.5	KET-LYS	69
Propyl Acetate	0.5	KET-LYS	70
p-Xylene	5.0	KET-LYS	31
Toluene	1.5	KET-LYS	32

2.c.ii CRYSTALLIZATION FROM KETOPROFEN SOLUTION WITH EQUIVALENT RATIO KET:LYS 3:1

In case of Acetone, Chloroform, Cyclopentanone, 1,4-Dioxane, Dimethyl Sulphoxide, Ethanol, Methanol, 1-Methyl-2-Pyrrolidone and Tetrahydrofuran, 150 mg of Ketoprofen (3 eq.) were completely dissolved in 0.5 mL of the proper solvent, then the solution was added to 29 mg (0.198 mmol) of Lysine. The mixture was so stirred for 24 hours at room temperature, and the obtained solid was isolated and analyzed by XRPD.

When no solid material precipitated after 24 hours, the clear solution was left to evaporate until the formation of a solid was observed.

The results of these experiments are collected in Table 3B:

Table 3B

Solvent	Stoichiometric ratio Ketoprofen : Lysine	Volume of Ketoprofen solution (mL)	XRPD	Yield
Acetone	3:1	0.5	KET-LYS	73
Chloroform	3:1	0.5	KET-LYS	75
Cyclopentanone	3:1	0.5	KET-LYS	69
1,4-Dioxane	3:1	0.5	KET-LYS	51
DMSO	3:1	0.5	KET-LYS	52
Ethanol	3:1	0.5	KET-LYS	85
Methanol	3:1	0.5	KET-LYS	75
1-Methyl-2-Pyrrolidone	3:1	0.5	KET-LYS	68
Tetrahydrofuran	3:1	0.5	KET-LYS	50
Acetone	2:1		No co-xx	--

Crystallization experiments in Benzyl Alcohol and Dichloromethane furnished a clear solution, therefore evaporation experiments were performed in order to collect a solid.

The solutions in Benzyl Alcohol was left to evaporate at high temperature (60 °C), while Dichloromethane solution was evaporated at room temperature.

Evaporation experiment of Benzyl Alcohol solution furnished Ketoprofen-Lysine co-crystal Form 1 with a yield of 80%. The evaporation of Dichloromethane solution led to the isolation of a sticky solid that was slurried in tert-Butyl methyl ether (TBME) for 24 hours; the obtained solid was obtained with a yield of 88% and was analyzed by XRPD, and the formation of Ketoprofen-Lysine co-crystal Form 1 was observed. XRPD patterns of the isolated solid are reported in Figure 3.

2.c.iii CRYSTALLIZATION FROM LYSINE AQUEOUS SATURATED SOLUTIONS.

The experiments were performed by preparing saturated solutions of racemic Lysine (ssLYS) in water. 650 mg of racemic Lysine were dissolved in 0.5 mL of water, then the solution was filtered and added to 87 mg (0.34 mmol) of Ketoprofen. The mixture was so stirred for 24 hours at room temperature; after this time, no solid was recovered, so the solution was left to evaporate at high temperature until the formation of a sticky solid was observed. In order to get a solid suitable for XRPD analysis, the sticky solid was slurried in Isopropyl Ether (IPE) for 24 hours. After this time, the formed solid was isolated and analyzed. Ketoprofen-Lysine co-crystal Form 1 was isolated by the experiment.

The results observed after these experiments are reported in the Table 3C.

Table 3C.

Results of crystallization experiments from Lysine saturated solution

Solvent	Volume of ssLYS (mL)	XRPD	Yield
Water	0.5	KET-LYS	80

2.d PREPARATION OF KETOPROFEN LYSINE SALT

Ketoprofen 0.76 g and racemic Lysine 0.44g (eq. ratio 1:1) were stirred in 20mL of methanol at 40°C for 1 hour. Ketoprofen was dissolved while the suspended Lysine was filtered off (filter 0.45um) directly in a Mettler Toledo Easymax 102 reactor. The solution was left under stirring for 5 minutes in the reactor, then 100mL of ethyl acetate was added and the solution was cooled down to -5°C without solid formation. Additional ethyl acetate (20 mL) was added through pipette in two aliquots (10mL and 10mL) to trigger the nucleation. The system was left under stirring until the suspension became milky. Additional 30 minutes of stirring was applied. The precipitate was then filtered and the collected sample was stored in a sealed vial at room temperature. The structure characterization XRPD (Figures 4, 5 and 6), FT-IR (Figures 10 and 12) and ^{13}C CPMAS solid-state NMR (Figures 8a and 8b) of the Ketoprofen-Lysine Salt in comparison with Ketoprofen-Lysine co-crystal Form 1 are reported.

3. XRPD ANALYSIS

The XRPD analysis has been carried out by using an instrumentation having the following characteristics:

Instrument type:	Rigaku MiniFlex600
Application SW:	Miniflex Guidance
Measurement Details	
Measurement type: Single scan	
Sample mode:	Reflection

Scan
Scan range: 3.000 – 40.000 ° (2θ)
Step size: 0.01 ° (2θ)
Speed: 10.0 °/min (2θ)
Scan mode: Continuous
Used wavelength
Intended wavelength type: Kα1
Kα1: 1.540598 Å
Kα2: 1.544426 Å
Kα2/Kα1 intensity ratio: 0.50
Kα: 1.541874 Å
Kα: 1.392250 Å
Instrument Details
X-Ray Generator
Tube output voltage: 40 kV
Tube output: 15 mA
High-voltage generation method: High-frequency Cockcroft-Walton method
Stability: Within ±0.05% for both the tube voltage and tube current, with reference to ±10% of input power variation.
X-ray tube
Name: Toshiba Analix type A-26L
Anode material: Cu
Maximus output: 0.60 kW
Focus size: 1 x 10 mm
Kβ Filter
Name: Ni-filter
Thickness (mm): 0.015
Material: Ni
Goniometer (Angle measuring device)
Type: Vertical θ/2θ
Goniometer radius: 150 mm
Scanning axis: θ/2θ linked
2θ scanning range: +2 ° to +140 °

θ/2θ axis minimum step angle:	0.005 ° (2θ)
Position speed:	500 °/min (2θ)
Scanning speed:	0.01 to 100 °/min
Datum angle:	2θ = 10 °
X-ray take-off angle:	6 ° (fixed)
Slit	
DS:	1.25 °
IHS:	10.0 mm
SS:	none (open)
RS:	none (open)
Incident side Soller slit:	2.5 °
Receiving side Soller slit:	2.5 °
Detector	
Name:	D/teX Ultra High-speed 1D Detector

A sample of the co-crystal Form 1 obtained with the process of crystallization from Ketoprofen in saturated solutions of Lysine (ssLYS) in water has been analyzed by XRPD in comparison with the XRPD spectra of Ketoprofen sodium Salt (CAS Registry Number 57495-14-4).

The XRPD spectra of Ketoprofen Lysine co-crystal Form 1 according to the invention is reported in Figure 4 and the characteristic peaks in Table 4.

The XRPD characteristic peaks of Ketoprofen sodium Salt are reported in Table 5A.

Table 4.

XRPD Peak List of Ketoprofen Lysine co-crystal Form 1

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.8993	435.68	0.1082	22.66049	4.13
7.6804	319.60	0.1181	11.51101	3.03
11.7158	278.42	0.1378	7.55366	2.64
13.7156	1526.54	0.0600	6.45110	14.46
13.7710	1327.16	0.0480	6.44127	12.57
14.7842	450.23	0.1680	5.98715	4.26
15.7842	336.90	0.1200	5.61000	3.19
16.2898	4583.06	0.1920	5.43702	43.41
16.6144	1424.36	0.0720	5.33150	13.49

17.4718	7614.33	0.1080	5.07176	72.12
17.5514	10557.15	0.0600	5.04892	100.00
17.6104	9822.64	0.0720	5.03214	93.04
17.6712	7012.09	0.0480	5.02744	66.42
18.8701	217.90	0.1920	4.69896	2.06
19.3117	2354.54	0.1080	4.59250	22.30
19.5987	6977.66	0.0840	4.52590	66.09
19.7109	7735.84	0.1320	4.50038	73.28
20.8279	4063.31	0.1440	4.26147	38.49
22.0196	3815.28	0.1680	4.03348	36.14
22.4475	447.39	0.1680	3.95754	4.24
23.0611	1200.74	0.1080	3.85360	11.37
23.5588	498.90	0.1920	3.77332	4.73
24.6240	876.89	0.0720	3.61244	8.31
25.0036	1224.58	0.0960	3.55846	11.60
25.3727	529.13	0.0960	3.50752	5.01
26.2107	2232.63	0.1200	3.39724	21.15
26.3276	3781.57	0.0600	3.38242	35.82
26.3865	3564.35	0.0840	3.37501	33.76
26.9304	489.50	0.2640	3.30807	4.64
27.5007	1267.34	0.0960	3.24075	12.00
27.5788	1386.90	0.0720	3.23175	13.14
27.6230	1185.72	0.0720	3.22668	11.23
28.0211	1840.86	0.1080	3.18174	17.44
28.4062	652.51	0.2160	3.13947	6.18
29.3372	771.26	0.1200	3.04193	7.31
29.5194	1030.48	0.2160	3.02356	9.76
30.1298	113.25	0.4320	2.96368	1.07
30.7515	45.91	0.2880	2.90516	0.43
32.2024	158.44	0.1680	2.77751	1.50
32.8514	229.15	0.1680	2.72410	2.17
33.4488	163.22	0.1920	2.67680	1.55
34.1115	1217.95	0.0840	2.62630	11.54

34.6158	332.37	0.1680	2.58919	3.15
34.7300	425.65	0.1200	2.58093	4.03
35.4285	350.71	0.2400	2.53163	3.32
35.7591	668.08	0.2160	2.50898	6.33
36.3198	513.39	0.0960	2.47152	4.86
36.4408	808.53	0.1440	2.46359	7.66
37.1144	32.86	0.2880	2.42041	0.31
38.2975	350.86	0.1920	2.34832	3.32
39.0372	313.47	0.1920	2.30550	2.97

Table 5A.

XRPD Peak List of Ketoprofen sodium Salt

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.2586	58.99	0.5510	16.80562	0.84
7.2447	7017.84	0.0886	12.20231	100.00
9.7739	54.29	0.1181	9.04963	0.77
10.7910	1811.29	0.1181	8.19887	25.81
13.3605	224.36	0.1378	6.62726	3.20
14.4207	221.78	0.1181	6.14233	3.16
15.7393	168.00	0.1181	5.63057	2.39
16.9104	512.57	0.1378	5.24320	7.30
18.1048	1322.27	0.0590	4.89990	18.84
18.7327	2418.71	0.1378	4.73704	34.47
19.1137	913.52	0.0984	4.64348	13.02
20.0517	819.98	0.0689	4.42833	11.68
21.0303	75.17	0.1968	4.22442	1.07
21.7191	2660.00	0.1476	4.09197	37.90
22.2315	3671.74	0.1378	3.99880	52.32
24.0819	161.01	0.1574	3.69558	2.29
24.4439	1377.06	0.0492	3.64166	19.62
24.8847	991.31	0.0984	3.57814	14.13
25.8156	33.53	0.2362	3.45120	0.48

26.5949	981.68	0.0689	3.35181	13.99
28.6755	268.69	0.1574	3.11317	3.83
28.9483	354.20	0.1181	3.08445	5.05
29.4014	284.97	0.1378	3.03794	4.06
29.6661	166.79	0.1574	3.01143	2.38
30.1057	202.66	0.1200	2.96599	2.89
30.2379	166.25	0.0840	2.96067	2.37
30.8737	141.72	0.1200	2.89394	2.02
31.2763	173.20	0.1680	2.85760	2.47
31.8620	298.97	0.1080	2.80640	4.26
32.4025	391.67	0.0960	2.76080	5.58
32.6399	229.39	0.1920	2.74127	3.27
33.2691	115.00	0.1440	2.69085	1.64
33.5904	299.42	0.1920	2.66584	4.27
34.9676	150.96	0.2640	2.56394	2.15
35.5019	152.56	0.2880	2.52656	2.17
36.2066	464.87	0.2880	2.47899	6.62
37.7949	190.00	0.1920	2.37838	2.71
38.2957	88.60	0.1920	2.34842	1.26
38.9966	81.76	0.1920	2.30781	1.16
39.4739	29.24	0.1920	2.28100	0.42

The XRPD diffractograms showed relevant signals in the region from 17 to 25° 2theta, in particular Ketoprofen sodium Salt showed the most intense peaks at 7.2447; 10.7910; 18.7327; 21.7191; 22.2315° 2theta, while Ketoprofen Lysine co-crystal Form 1 according to the invention at 16.2898; 17.4718, 17.5514; 17.6104; 17.6712; 19.5987; 19.7109° 2theta.

The XRPD spectra of Ketoprofen Lysine Salt in comparison with the XRPD spectra of Ketoprofen Lysine Co-crystal Form 1 is shown in Figure 6 while the characteristic XRPD peaks of Ketoprofen Lysine Salt are reported in Table 5B below:.

Table 5B:

XRPD Peak List of Ketoprofen Lysine Salt

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.9325	2846.60	0.1476	22.46912	100.00
7.8614	122.69	0.1181	11.24637	4.31
8.5371	92.20	0.1181	10.35764	3.24
9.1615	141.64	0.1968	9.65313	4.98
11.0605	527.66	0.1181	7.99966	18.54
11.8024	131.06	0.2362	7.49843	4.60
13.0204	1516.34	0.0689	6.79958	53.27
14.1357	181.38	0.1968	6.26551	6.37
15.0097	72.85	0.1968	5.90258	2.56
17.4211	652.89	0.1574	5.09063	22.94
18.8604	2197.33	0.0689	4.70525	77.19
19.4898	678.61	0.1181	4.55471	23.84
20.9970	1941.40	0.0787	4.23104	68.20
21.4845	2046.59	0.1378	4.13613	71.90
22.2596	1258.41	0.1771	3.99383	44.21
22.9984	616.52	0.0787	3.86717	21.66
23.6473	222.80	0.2362	3.76250	7.83
24.6845	207.27	0.3149	3.60672	7.28
25.8298	707.10	0.0787	3.44933	24.84
26.6005	977.38	0.0886	3.35111	34.34
28.3958	134.48	0.1574	3.14320	4.72
29.2001	419.42	0.1771	3.05843	14.73
30.7454	46.23	0.3149	2.90814	1.62
31.9837	376.56	0.1378	2.79832	13.23
32.7583	225.02	0.1574	2.73389	7.90
33.5545	173.12	0.2362	2.67082	6.08
35.3568	377.39	0.1378	2.53870	13.26
36.6756	185.11	0.2755	2.45038	6.50
38.3677	278.83	0.3149	2.34612	9.80

The XRPD diffractograms showed relevant signals in the region from 13 to 27° 2theta, in particular Ketoprofen Lysine Salt showed the most intense peaks at

13.0204, 17.4211, 18.8604, 19.4898, 20.9970, 21.4845 and 26.6005° 2theta, while Ketoprofen Lysine co-crystal Form 1 according to the invention at 16.2898; 17.4718, 17.5514; 17.6104; 17.6712; 19.5987; 19.7109° 2theta.

4. Solid State NMR

Solid-state NMR (ss-NMR) spectra were acquired with a Bruker Avance II 400 Ultra Shield instrument, operating at 400.23, 100.63 and 40.56 MHz, respectively for ^1H, ^{13}C and ^{15}N nuclei. Powder samples were packed into cylindrical zirconia rotors with a 4 mm o.d. and an 80 µL volume. A certain amount of sample was collected and used without further preparations to fill the rotor.

^{13}C CPMAS (cross polarized magic angle spinning) solid-state NMR spectra were acquired at a spinning speed of 12 kHz, using a ramp cross-polarization pulse sequence with ss-NMR spectra were acquired with a Bruker Avance II 400 Ultra Shield instrument, operating at 400.23, 100.63 and 40.56 MHz, respectively for ^1H, ^{13}C and ^{15}N nuclei.

Powder samples were packed into cylindrical zirconia rotors with a 4 mm o.d. and an 80 µL volume. A certain amount of sample was collected and used without further preparations to fill the rotor.

^{13}C CPMAS solid-state NMR spectra were acquired at a spinning speed of 12 kHz, using a ramp cross-polarization pulse sequence with a 90° 1H pulse of 3.60 µs, a contact time of 3 ms, optimized recycle delays between 1.5 and 3.5 s, a number of scans in the range 430-640, depending on the sample.

^{15}N CPMAS spectra were acquired at a spinning speed of 9 kHz using a ramp cross-polarization pulse sequence with a 90° ^1H pulse of 3.60 µs, a contact time between 1 and 4 ms, optimized recycle delays between 1.1 and 3.4 s, a number of scans in the range 14330-22770, depending on the sample.

For every spectrum, a two-pulse phase modulation (TPPM) decoupling scheme was used, with a radiofrequency field of 69.4 kHz. The ^{13}C chemical shift scale was calibrated through the methylene signal of external standard glycine (at 43.7 ppm). The ^{15}N chemical shift scale was calibrated through the signal of external standard glycine (at 33.4 ppm with reference to NH_3).

2D $^1H-^{13}C$ on- and off-resonance (short and long-range, respectively) HETCOR spectra were measured with contact times of 0.1 and 7 ms, respectively, and FSLG t1 decoupling and TPPM t2 decoupling (rf fields of 82 kHz).

288 and 384 scans were averaged for 88 and 128 increments, respectively with 3.4 s of relaxation delay. The indirect ^{1}H chemical shift scale in the HETCOR spectra was experimentally corrected by a scaling factor of 1/3 because the ^{1}H chemical-shift dispersion is scaled by a factor of 1/3 during FSLG decoupling.

The ^{13}C CPMAS solid-state NMR spectra of co-crystal Form 1 according to the invention is reported in Figure 7.

The ^{13}C CPMAS solid-state NMR spectra of comparative Ketoprofen Lysine Salt is reported in Figure 8a.

The ^{13}C CPMAS solid-state NMR spectra of Ketoprofen Lysine Salt in comparison with Ketoprofen Lysine Co-crystal Form 1, Ketoprofen and Lysine is reported in Figure 8b.

As appears from the spectra of Figure 8b, the resonances of both Ketoprofen Lysine Salt and Ketoprofen Lysine Co-crystal Form 1 differ from the characteristic signals of both the starting materials Ketoprofen and Lysine.

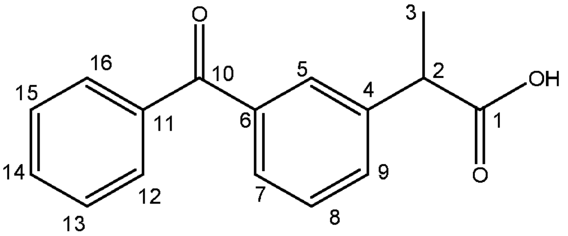
The main differences in the spectra of Ketoprofen Lysin Salt compared to Ketoprofen Lysine Co-crystal Form 1 are mostly in the set of interaction involving the carboxylic group of Ketoprofen and Lysine. The three signals of the carboxylic group ascribed to Ketoprofen (182.2, 181.1 and 180.0 ppm, Figure 8b) of the species Ketoprofen Lysine Salt are consistent with the deprotonated nature of the carboxylic group while the signal of the un-dissociated COOH group of Ketoprofen in the Ketoprofen Lysine Co-crystal Form 1 structure falls below 180 ppm.

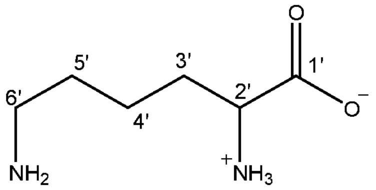
Table 6A and Table 6B. The assignment of the peaks in ^{13}C CPMAS solid-state NMR of Ketoprofen Lysine co-crystal Form 1, Ketoprofen Sodium Salt and Ketoprofen Lysine Salt are reported herein below:

Table 6A

Ketoprofen Lysine co-crystal Form 1		Ketoprofen Sodium Salt	
^{13}C δ (ppm)	C atom	^{13}C δ (ppm)	C atom
196.1	10	200.6	10a
177.6	1	200.1	10b
174.5	1'	181.4	1a
147.4	Aromatic C_q (6 or 11 or 4)	180.5	1b

141.0	Aromatic C_q (6 or 11 or 4)	144.2	Aromatic C_q
134.8	Aromatic C_q (6 or 11 or 4)	141.6	Aromatic C_q
133.0	Aromatic CH	139.4	Aromatic C_q
128.8	Aromatic CH	138.4	Aromatic C_q
128.3	Aromatic CH	132.3	Aromatic CH
128.0	Aromatic CH	130.0	Aromatic CH
126.8	Aromatic CH	128.9	Aromatic CH
55.1	2'	128.1	Aromatic CH
50.2	2	123.2	Aromatic CH
38.8	6'	122.9	Aromatic CH
32.2	5'	51.0	2a
29.6	3'	49.0	2b
24.7	3	22.0	3a
22.3	4'	14.4	3b





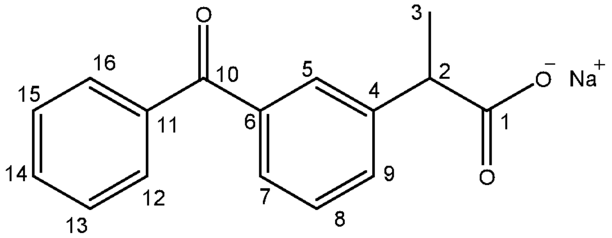


Table 6B:

^{13}C CPMAS solid-state NMR peak list of Ketoprofen Lysine Salt.

Ketoprofen Lysine Salt	
^{13}C δ (ppm)	^{13}C δ (ppm)
199.8	127.2

197.8	125.9
182.2	564
181.1	55.5
180.0	20.8
176.6	49.4
175.7	48.2
174.3	38.6
144.5	38.2
143.8	32.3
142.7	31.7
138.2	26.4
134.6	25.7
131.8	22.5
129.5	22.0
128.6	

Table 6B shows the peak list of the characteristic signals of the Ketoprofen Lysine Salt. The average full width at half-maximum value (133 Hz) is consistent with a moderately crystalline phase. The carboxylic signals infer a 1:1 ratio between Ketoprofen and Lysine.

Possibly six independent molecules in the unit cell are evaluable by ^{13}C CPMAS solid-state NMR spectra: the carboxylic signals infer the presence of 3 carboxylate moieties for both Ketoprofen and Lysine.

5. FT-IR and FT-Raman

FT-IR: The analysis was carried out using a Thermo Nicolet iS50 - ATR module Spectrometer equipped with:

- Smart Performer Diamond
- DTGS KBr Detector
- IR Source
- KBr Beam splitter

Data Collection Information

Number of sample scans: 32

Number of background scans 32

Collection length: 47, 29 sec

Resolution: 4,000

Levels of zero filling: 2

Number of scan points: 16672

Number of FFT points: 65536

Laser frequency: 15798, 3 cm^{-1}

Interferogram peak position: 8192

Apodization: N-B strong

Phase correction: Mertz

Number of background scans: 32

Background gain: 1,0

Sample gain: 8

Aperture 100

Optical velocity 0.6329

FT-Raman spectra were recorded with a Nicolet iS50 FT-IR Spectrometer. The excitation source was a Nd-YAG laser (1064 nm) in the backscattering (180°) configuration. The focused laser beam diameter was approx. 50 mm and the spectral resolution 4 cm^{-1}. The spectra were recorded with a laser power at the sample of approx. 100 mW.

FT-IR spectrum and FT-Raman spectrum of Ketoprofen Lysine co-crystal Form 1 according to the invention and their peak list are reported in the Figures 10, 11 and in Tables 7 and 8, respectively.

FT-IR and FT-Raman peak list of Ketoprofen Lysine sodium Salt are reported in Tables 9A and 10 respectively.

FT-IR spectrum and FT-Raman spectrum of Ketoprofen Lysine Salt and the peak list are reported in the Figures 12 and 11 and Table 9B respectively.

Table 7.

Peak list of the FT-IR spectrum of Ketoprofen Lysine co-crystal Form 1

Peak List		1022	78.405	2679	77.361
		1043	89.951	2817	73.411
Position	Intensity	1070	80.462	2858	72.192
412	70.137	1083	82.338	2919	73.338
441	77.258	1101	85.567	2962	74.418
448	80.669	1138	68.451	3055	85.101

486	45.930	1158	87.896	3170	89.842
549	73.524	1175	74.914		
620	54.809	1197	73.233		
651	69.299	1223	79.989		
666	65.871	1247	59.043		
687	56.786	1273	41.449		
696	62.440	1286	42.036		
708	46.485	1315	50.763		
715	43 933	1331	69.556		
731	84.532	1352	51.614		
784	72.134	1364	66.337		
797	70.060	1398	37.374		
815	76.999	1431	73.698		
825	77.325	1448	64.543		
832	81.431	1455	58.033		
852	76.991	1484	60.127		
872	72.342	1542	51.389		
882	58.800	1577	39.398		
895	86.893	1586	39.616		
935	93.097	1631	54.419		
971	73.456	1665	52.612		
1003	77.074	2601	78.326		

Table 8.

Peak list of the FT-Raman spectrum of Ketoprofen Lysine co-crystal Form 1

Peak list:		1286	10.733
		1314	11.948
Position	Intensity	1338	8.344
405	4.079	1405	8.461
433	4.149	1440	9.612
489	8.298	1462	8.437
552	3.812	1485	3.668
619	12.034	1545	3.946

652	5.582	1596	60.158
699	12.319	1664	53.818
709	17.337	2563	3.628
850	7.016	2628	4.547
874	9.894	2673	4.168
934	5.214	2713	5.167
972	8.158	2737	5.915
1002	78.866	2765	6.224
1028	12.588	2866	19.637
1043	5.890	2922	53.412
1076	9.388	2967	31.934
1137	14.158	3027	14.424
1169	13.919	3064	67.759
1182	13.473	3128	5.228
1193	23.310	3155	5.872
1247	7.418	3200	4.431

Table 9A.

Peak list of the FT-IR spectrum of Ketoprofen sodium Salt

Position (cm^{-1})	Intensity	Position (cm^{-1})	Intensity
429	47.958	1141	81.367
450	67.736	1175	65.123
485	62.079	1197	72.826
581	59.026	1243	44.516
608	49.504	1258	49.940
645	20.703	1276	36.862
674	45.042	1296	43.082
688	21.598	1321	34.820
701	20.966	1363	50.753
719	25.875	1397	26.410
784	45.878	1445	58.051
805	72.985	1462	73.435

822	67.726	1477	84.257
841	64.615	1570	16.521
884	42.140	1582	19.151
932	81.401	1656	37.290
953	59.710	2874	96.175
999	81.442	2912	91.001
1020	82.601	2931	92.937
1030	85.312	2966	87.542
1068	70.099	3062	93.322
1104	84.982	3386	91.434

Table 9B.

Peak list of the FT-IR spectrum of Ketoprofen Lysine Salt

Position (cm^{-1})	Intensity	Position (cm^{-1})	Intensity
414	51.203	1160	79.502
437	69.203	1179	81.151
463	76.990	1201	81.656
475	76.368	1248	65.816
518	63.818	1281	53.933
539	60.253	1320	58.117
621	69.700	1358	59.706
645	61.177	1393	53.834
675	72.596	1420	69.095
689	66.858	1448	68.893
706	55.062	1479	72.920
713	56.968	1532	44.203
756	82.432	1538	43.543
779	73.315	1557	42.899
802	80.054	1615	73.015
821	87.571	1652	65.459
831	88.245	2050	95.210
871	69.950	2089	95.059
911	88.295	2112	94.226

929	90.674	2324	93.704
958	84.976	2650	84.309
967	88.368	2879	75.764
1007	80.471	2942	72.790
1072	84.876	3420	95.023
1138	77.764		

Table 10.

Peak list of the FT-Raman spectrum of Ketoprofen sodium Salt

Position (cm^{-1})	Intensity	Position (cm^{-1})	Intensity
102	1160.009	1196	219.581
165	474.578	1246	59.734
224	262.371	1292	39.549
291	80.737	1317	43.223
405	38.647	1407	54.635
431	39.619	1459	48.167
615	65.766	1597	535.213
701	114.002	1664	392.191
722	46.145	2874	54.582
786	37.023	2910	121.051
885	71.029	2932	111.658
1001	574.704	2965	109.112
1026	140.789	3025	63.116
1140	77.492	3061	362.268
1160	89.545		

6. DSC ANALYSIS

The analysis was carried out using a DSC Mettler Toledo DSC1.

The samples of Ketoprofen Lysine co-crystal Form 1 and of Ketoprofen Lysine Salt were weighed in an aluminum pan hermetically sealed with an aluminum cover. The analysis was performed heating the sample from 25°C to 320°C at 10 K/min.

Temperature data

Temperature range	25°C to 320 °C

Temperature accuracy	± 0.2 K
Temperature precision	± 0.02 K
Heating rate	10 K/min
Cooling time	5 min (100°C … 0ºC)

Calorimetric Data

Sensor type	FRS5
Sensor material	Ceramic
Number of thermocouples	56
Signal time constant	1.8 s
Indium peak (height to width)	17
TAWN resolution	0.12
Sensitivity	11.9
Resolution	0.04 µW
Digital resolution	16.8 million points

DSC thermogram of Ketoprofen Lysine co-crystal Form 1 is reported in Figure 13.

The DSC thermogram of Ketoprofen Lysine co-crystal Form 1 shows an endothermic peak at onset temperature 164.14 °C.

DSC thermogram of Ketoprofen Lysine Salt is reported in Figure 14.

The DSC thermogram of Ketoprofen Lysine Salt shows:

- A first endothermic peak (54.67 J/g) onset 100,53°C, peak 110,92°C, endset 118,35°C.
- Above 120°C multiple partially overlapped endothermic peaks due to degradation steps.

7. DISSOLUTION RATE

The dissolution rate of Ketoprofen Sodium Salt and Ketoprofen Lysine co-crystal Form 1 have been analyzed.

Method

Product (25 mg powder sample) were tested in a USP39 Apparatus 2 (Distek Dissolution System 2100B) in 250 ml USP buffer pH 1.2, at 37°C and 100 rpm paddle rotation speed.

The amount of solid dissolved at each time point was determined spectrophotometrically at 260 nm.

The dissolution profiles (mean of 2 replicates) of Ketoprofen Lysine co-crystal Form 1 according to the invention and Ketoprofen Sodium Salt are shown in Figure 15.

Dissolution rate Ketoprofen Lysine co-crystal Form 1 (formulate)

Method

The dissolution test was performed in a Sotax AT7-smart dissolution apparatus equipped with the paddle arrangement according to 2018 edition of European Pharmacopoeia. The quantitative assay was determined by HPLC against external standard.

The dissolution was performed on Ketoprofen Lysine co-crystal Form 1 as a granulate with the following composition: Ketoprofen Lysine co-crystal Form 1 (Active Ingredient). Excipients: Mannitol, Povidone, Anhydrous colloidal silica, Sodium chloride, Sodium saccharin, Ammonium glycyrrhizinate, Mint flavor.

The dissolution medium was prepared dissolving 29.2 g of NaCl in about 3 liters of water, then 70.6 ml of HCl were added and diluted to 10 liters with water. The pH was adjusted to 1.2.

Approximately 76 mg of product were placed in each of the 6 vessels containing 1000 ml of the dissolution medium. At each sampling time 5 ml aliquot was withdrawn and filtered through 1.5 mm Wathman 934-AH filters. The filtered solution was injected in HPLC.

Instrumental condition:

- Apparatus: dissolution apparatus Sotax AT7-smart.
- Dissolution volume: 1000 ml.
- Temperature: 37 ± 0.5 °C.
- Rotation speed: 100 rpm.
- Sampling time: 5,10,15,20,30,45,60.

Solubility

The solubility of Ketoprofen Lysine co-crystal Form 1 at different pH is shown in Table 11 below. Ketoprofen Lysine co-crystal Form 1 has a solubility of 280 mg/mL at pH 6.8.

Table 11:

Solubility of Ketoprofen Lysine co-crystal Form 1 at different pH

pH	Solubility (mg/mL)
1.0	0.33
4.6	1.82
6.8	280.2

8. OTHER TESTS

Loss on drying Assay

The loss on drying of Ketoprofen Sodium Salt and Ketoprofen Lysine co-crystal Form 1 have been assessed in long term and accelerated conditions according to the 2018 of European Pharmacopoeia. The results are shown in the following Tables 12A and 12B.

Table 12A:

Long term conditions (25°C/60% RH)

Ketoprofen Sodium Salt						
		Storage (months)				
Test	Limits	0	3	6	9	12
Appearance	White powder	White powder	White powder	White powder	White powder	White powder
Loss on drying (%)	≤ 5.0 %	1.27	3.25	5.53	5.78	6.35
Ketoprofen Lysine co-crystal Form 1 (invention)						
		Storage (months)				
Test	Limits	0	3	6	9	12
Appearance	White powder	White powder	White powder	White powder	White powder	White powder
Loss on drying (%)	≤ 5.0 %	0.13	0.31	0.31	0.32	0.29

Table 12B:

Accelerated conditions (40°C/75% RH)

Ketoprofen Sodium Salt							
		Storage (months)					
Test	Limits	0	1	2	3	6	12
Appearance	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Loss on drying (%)	≤ 5.0 %	1.28	1.68	2.05	3.95	6.17	7.27
Ketoprofen Lysine co-crystal Form 1 (invention)							
		Storage (months)					
Test	Limits	0	1	2	3	6	12
Appearance	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Loss on drying (%)	≤ 5.0 %	0.13	0.34	0.27	0.49	0.48	0.50

Particle size distribution

Ketoprofen Lysine Co-crystal Form 1 and Ketoprofen Lysine Salt were analysed by Mastersizer laser diffraction. Particle size analysis is related to the rheological behaviour of the powder and to the dissolution rate of the product. A significant variation of the particle size between Ketoprofen Lysine Co-crystal Form 1 and Ketoprofen Lysine Salt was observed, as reported in the following Table 13:

Table 13.

Comparison between the PSD of Ketoprofen Lysine Co-crystal Form 1 and Ketoprofen Lysine Salt.

PSD	Ketoprofen Lysine Co-crystal Form 1	Ketoprofen Lysine Salt

D10 (μm)	4.4	84
D50 (μm)	82.0	131
D90 (μm)	192.3	348

Crystallinity

As demonstrated by the XRPD analysis, the Ketoprofen Lysine co-crystal Form 1 has a crystallinity significantly higher than the Ketoprofen Lysine Salt where the presence of amorphous phase is evident (Figure 17).

The lower particle size diameter of the present Ketoprofen Lysine co-crystal Form 1 combined with higher crystallinity can provide for many advantages in comparison with the previous Ketoprofen Lysine Salt. In fact, particle size distribution plays an important part in the production process (quality control) and in the development of suitable manufacturing methods. Smaller final mean particle sizes can improve content uniformity, solubility, dissolution, absorption rates and bioavailability.

A further advantage of the present Ketoprofen Lysine Co-Crystal Form 1 compared with the previous Ketoprofen Lysine Salt is that it can be obtained directly from the crystallization step in a lower particle size, thus minimizing or even avoiding downstream micronization of the powder in order to get the desired particle size diameter, with a potential reduction of process steps, time and, in the end, manufacturing costs.

Finally, the superior crystallinity of the present Ketoprofen Lysine co-crystal Form 1 compared with Ketoprofen salts such as Ketoprofen Sodium or Lysine Salt is advantageous in terms of increased stability of the product.

CLAIMS

1. Co-crystal of Ketoprofen Lysine Form 1 characterized by having an X ray diffraction pattern with characteristic peaks at 16.3; 17.5; 17.6; 17.7; 19.6; 19.7° 2theta ± 0.20 degrees.

2. The co-crystal according to claim 1, characterized by having a X ray diffraction pattern as represented in Figure 4.

3. The co-crystal according to claim 1 or 2, wherein the molecular ratio between Ketoprofen and Lysine is 1:1.

4. The co-crystal according to any one of claims 1 to 3, wherein said co-crystal is selected from the group consisting of: (R)-2-(3-benzoylphenyl)-propionic acid D-Lysine, (R)-2-(3-benzoylphenyl)-propionic acid L-Lysine, (S)-2-(3-benzoylphenyl)-propionic acid D-Lysine and (S)-2-(3-benzoylphenyl)-propionic acid L-Lysine.

5. The co-crystal according to any one of claims 1 to 4 having a particle size distribution with a D90 lower than 300 μm, preferably lower than 250 μm, more preferably lower than 200 μm.

6. A pharmaceutical composition comprising the co-crystal of any one of the preceding claims and one or more physiologically acceptable excipients.

7. The pharmaceutical composition according to claim 6, wherein said excipients are selected from the group consisting of:

povidone, colloidal silica, hydroxypropylmethylcellulose, eudragit EPO, sodium dodecyl sulfate, stearic acid, magnesium stearate, aspartame, mannitol, xylitol, talc, flavors.

8. The pharmaceutical composition of claim 6 or 7, wherein said pharmaceutical composition is in solid granulate form.

9. A pharmaceutical composition comprising the co-crystal of Ketoprofen Lysine Form 1 according to any one of claims 1 to 5 in combination with one or more pharmaceutically active agents.

10. The co-crystal of Ketoprofen Lysine Form 1 and the pharmaceutical composition of any one of the preceding claims for use as a medicament.

11. The co-crystal and the pharmaceutical composition of any one of the preceding claims, for use in the treatment of pain and inflammation diseases.

12. The co-crystal and pharmaceutical composition for use according to claim 11, wherein said pain is selected from the group consisting of: acute pain, headache, toothache, menstrual pain, muscle pain, osteoarticular pain.

13. The co-crystal and pharmaceutical composition for use according to claim 11, wherein said inflammation diseases is selected from the group consisting of rheumatitis disease.

14. A process for the production of co-crystal of Ketoprofen Lysine Form 1 comprising the step of:

a) preparing a saturated solution of Ketoprofen;
b) mixing the saturated solution with Lysine;

or

a_1) preparing a saturated solution of Lysine in water;
b_1) mixing the saturated solution with Ketoprofen.

15. The process according to claim 14, wherein the equivalent ratio between saturated Ketoprofen and Lysine or between saturated Lysine and Ketoprofen is 3:1 or higher.

16. The process according to claim 14, comprising the steps a) and b), wherein the equivalent ratio between Ketoprofen in the saturated solution and Lysine is from 10:1 to 1:1, more preferably from 3:1 to 1:1.

17. The process according to claim 14, comprising the steps a) and b), wherein the ratio between the amount of Lysine by weight (mg) and the volume (ml) of the saturated solution of Ketoprofen is comprised between 1 mg/ml and 90 mg/ml, preferably from 4 mg/ml to 70 mg/ml, more preferably from 5 mg/ml to 60 mg/ml.

18. The process according to any one of claims 14 to 17, wherein the solvent used for the saturated solution of Ketoprofen is selected form the group consisting of: alcohols, ethers, esters, amides, ketones, aromatic solvents, halogenated solvents and aprotic dipolar solvents.

19. The process according to claim 18, wherein the solvent used for the saturated solution is selected from the groups of:

- alcohols, wherein said alcohols are selected from the group consisting of: ethanol, methanol, 1-butanol, 1-propanol, 2-butanol, 2-propanol, 1-pentanol and benzyl alcohol;
- ethers, wherein said ethers are selected from the group consisting of: 1,4-dioxane, tetrahydrofuran;

- esters, wherein said esters are selected from the group consisting of: ethyl acetate, methyl acetate, propyl acetate;

- amides, wherein said amides are selected from the group consisting of: N,N, dimethylacetamide, 1-methyl-2-pirrolidone;

- ketones, wherein said ketones are selected from the group consisting of: acetone, cyclopentanone, 4-Methyl-2-Pentanone.

- aromatic solvents, wherein said aromatic solvents are selected from the group consisting of: toluene, benzonitrile, p-xylene;

- halogenated solvents, wherein said halogenated solvents are selected from the group consisting of: dichloromethane, 1,2-dichloroethane and chloroform; or

- aprotic dipolar solvents, wherein said aprotic dipolar solvents are selected from the group consisting of: dimethylsulphoxide, acetonitrile, and their admixtures.

20. The process according to any one of claims 14 to 19, wherein said mixing step b) or b_1) is carried out a temperature from 15°C to 30°C, for 10 to 72 hours, more preferably at room temperature for 24 hours.

Figure 1

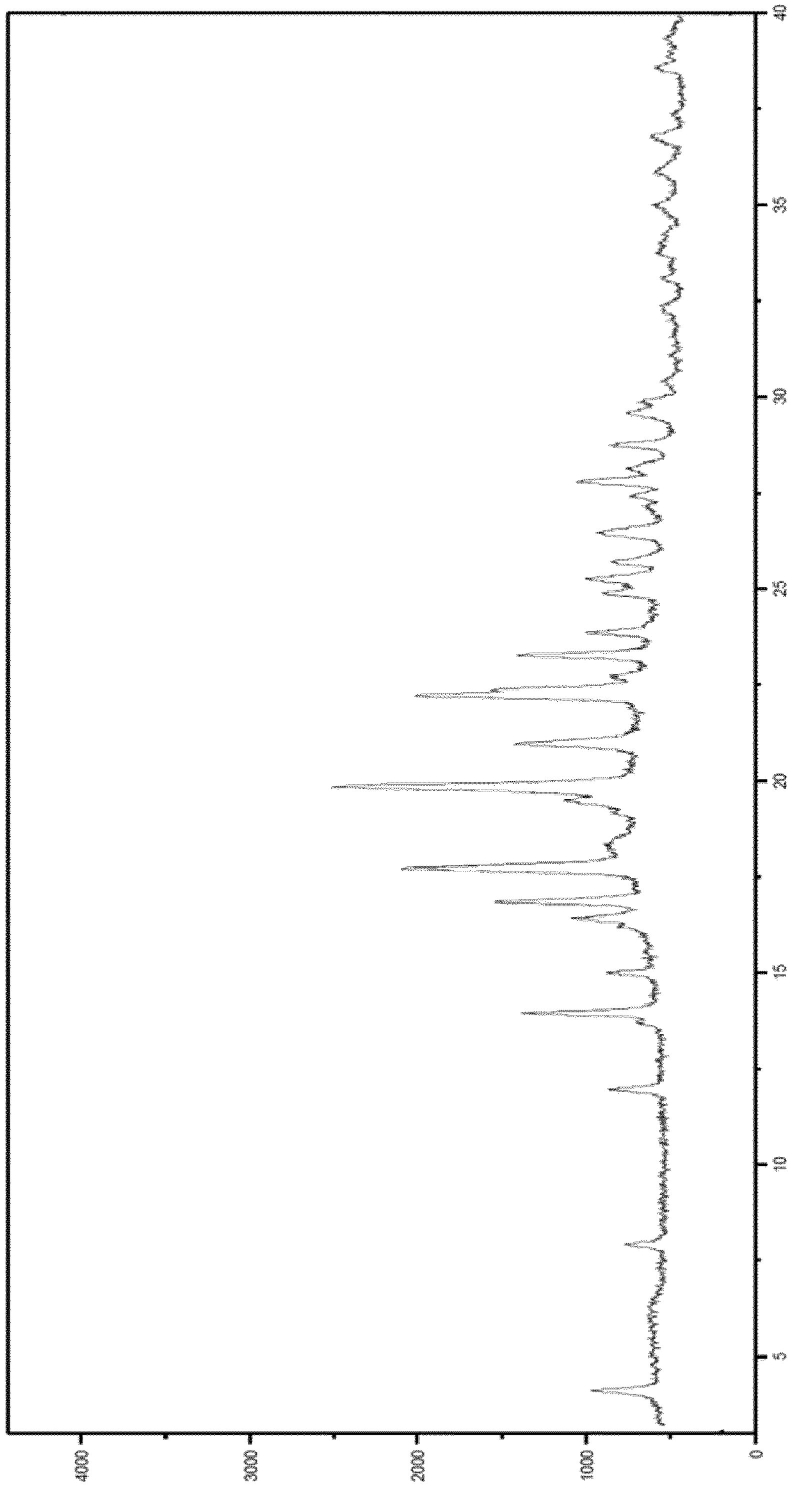


Figure 2

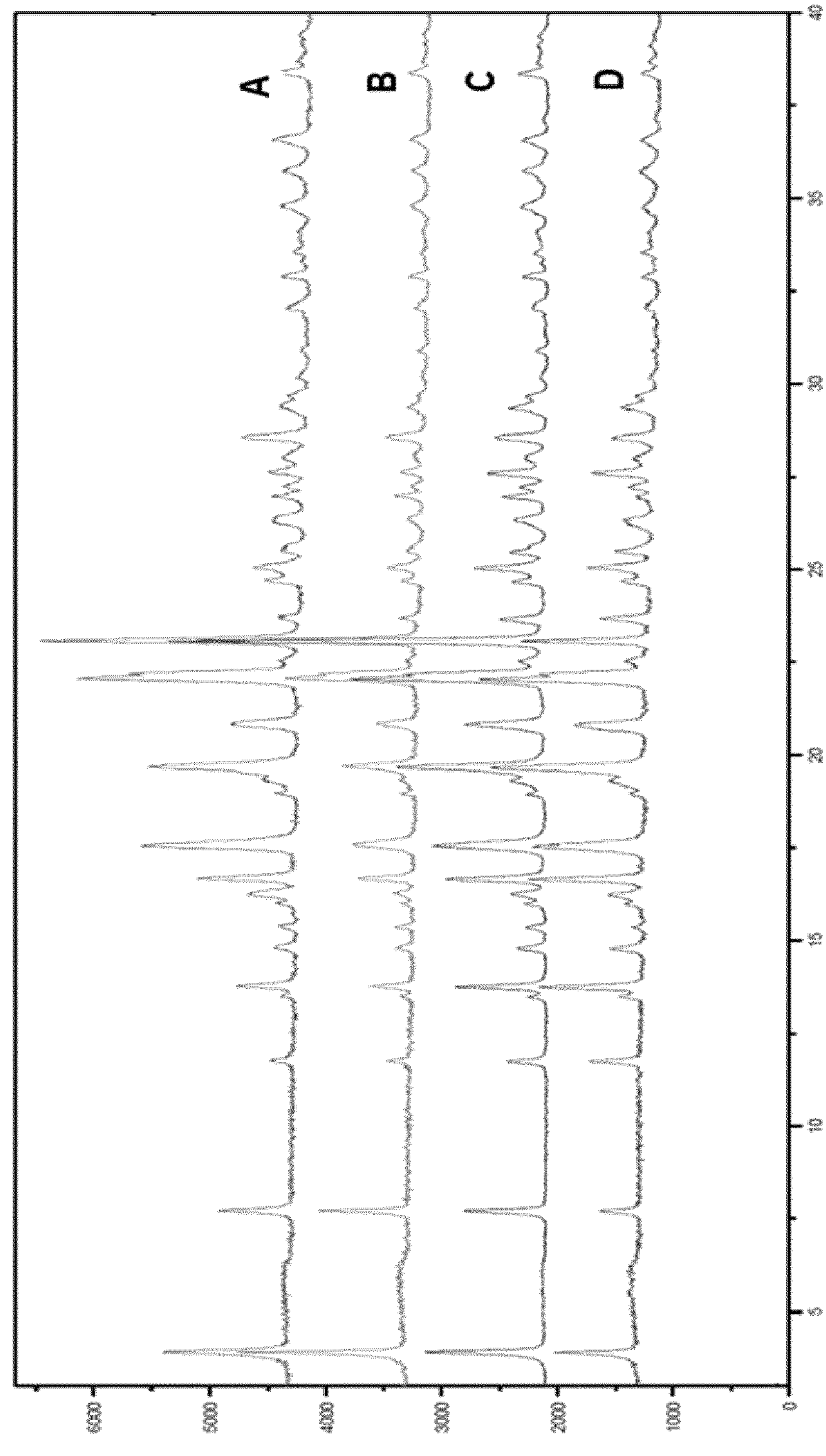


Figure 3

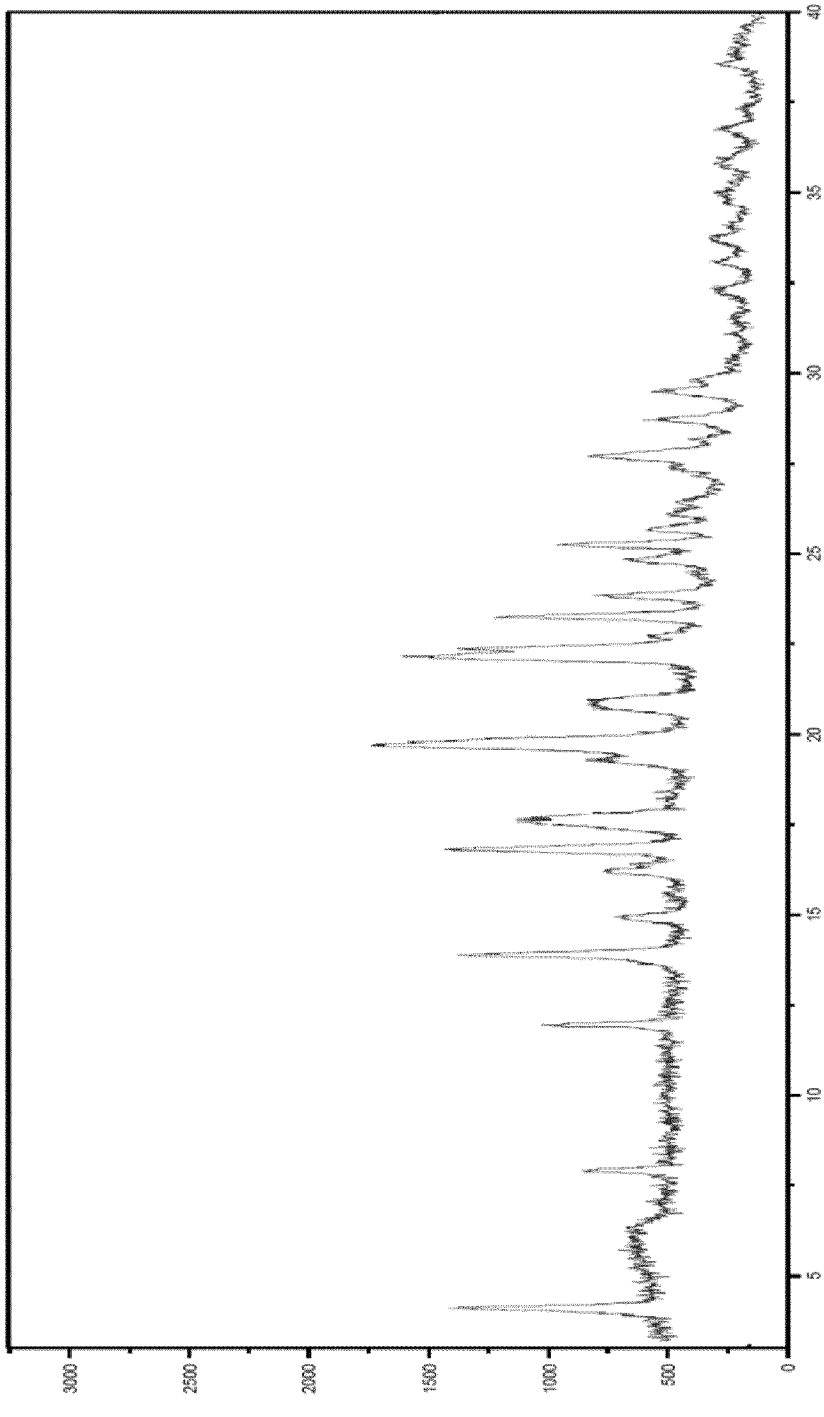
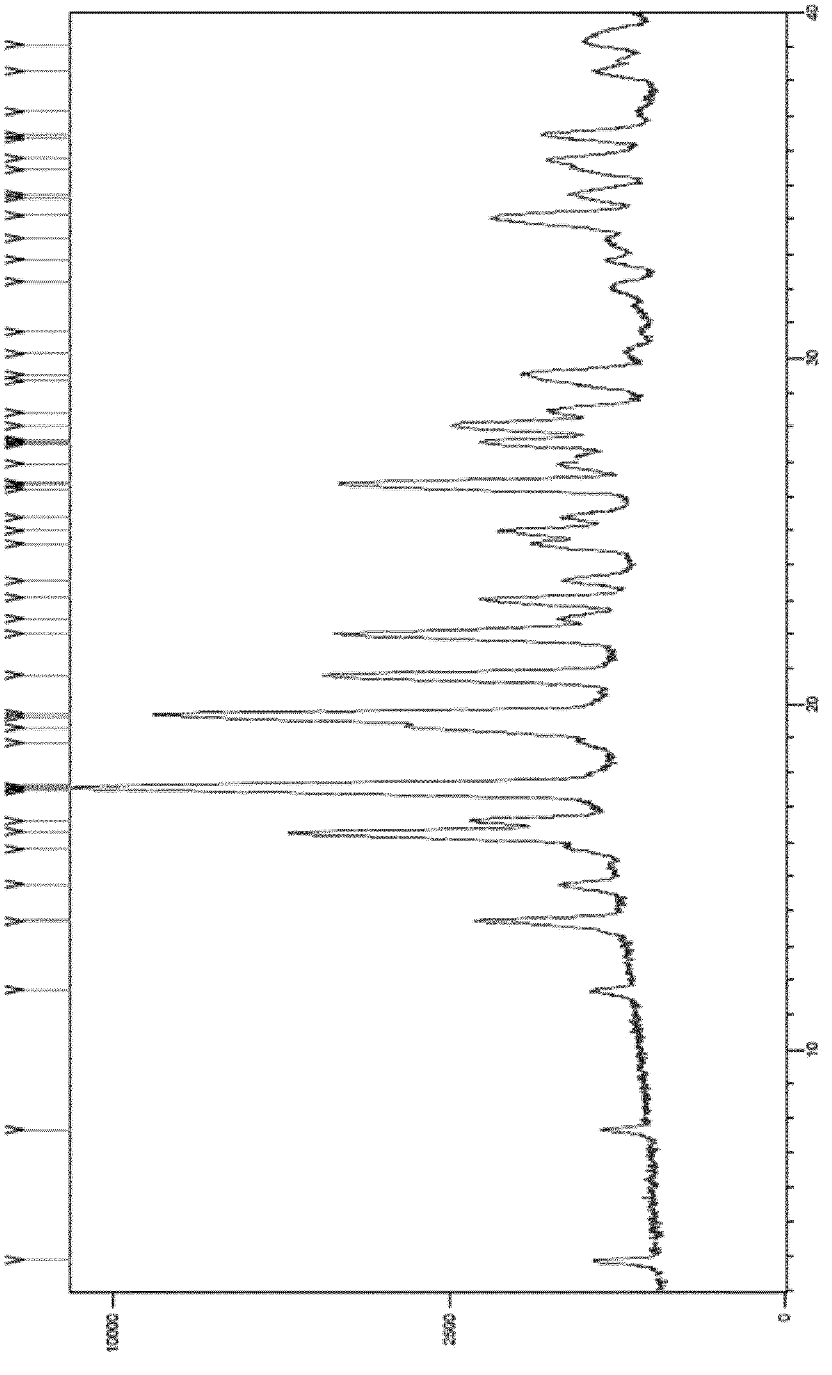


Figure 4



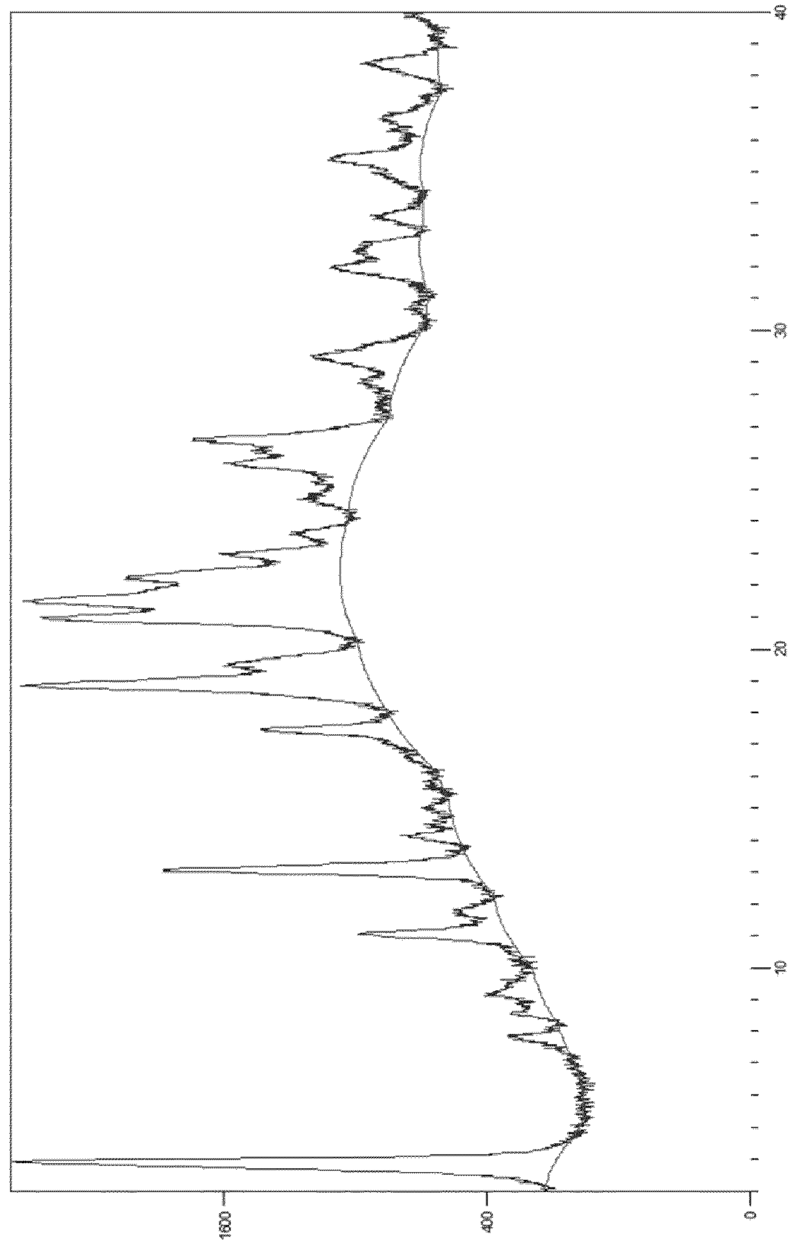
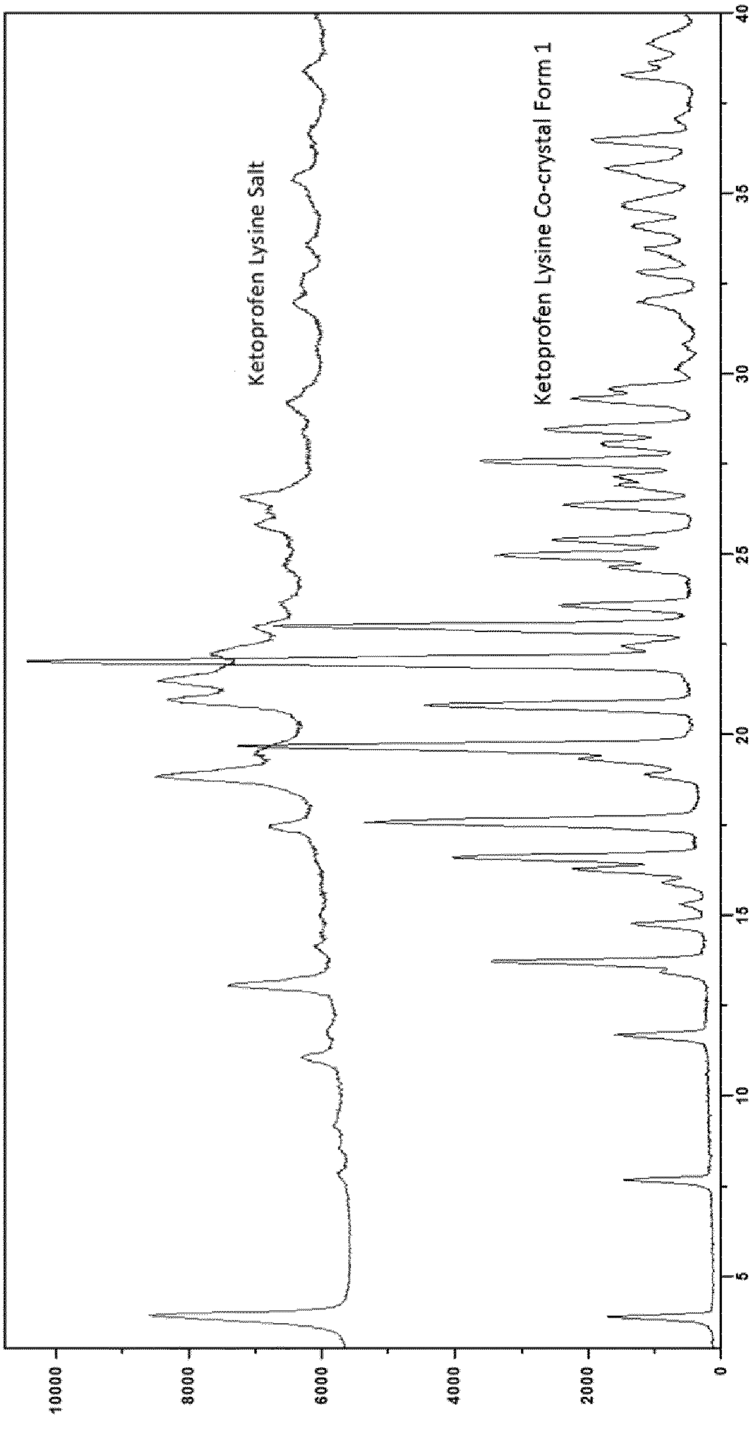


Figure 5

Figure 6


Ketoprofen Lysine Salt
Ketoprofen Lysine Co-crystal Form 1
0
2000
4000
6000
8000
10000
5
10
15
20
25
30
35
40

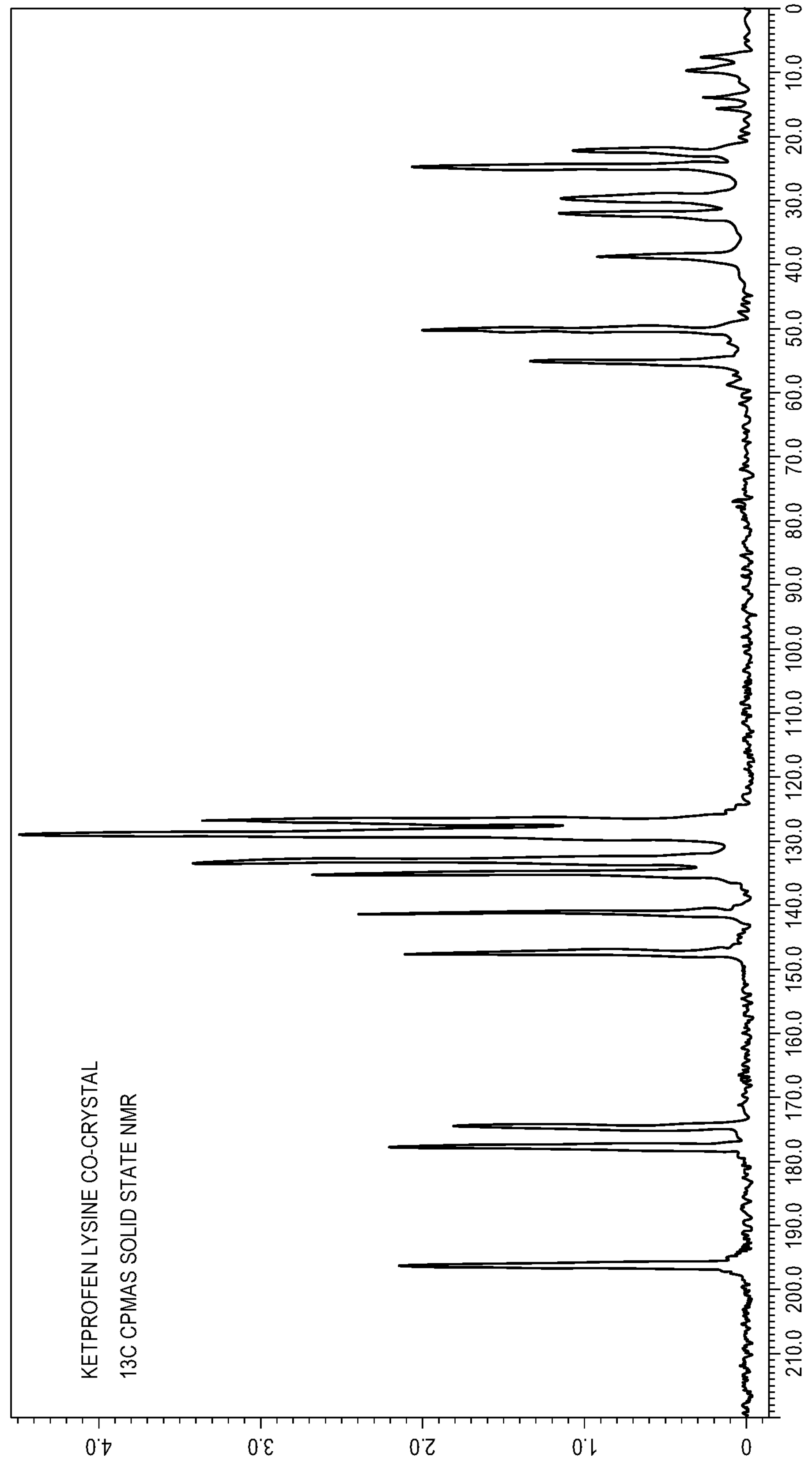
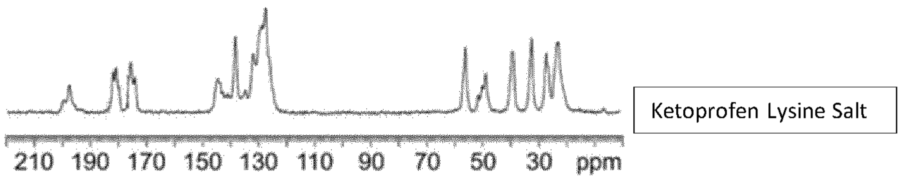

KETPROFEN LYSINE CO-CRYSTAL
13C CPMAS SOLID STATE NMR
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0
190.0
200.0
210.0
0
1.0
2.0
3.0
4.0

FIG. 7

Figure 8

8a



8b

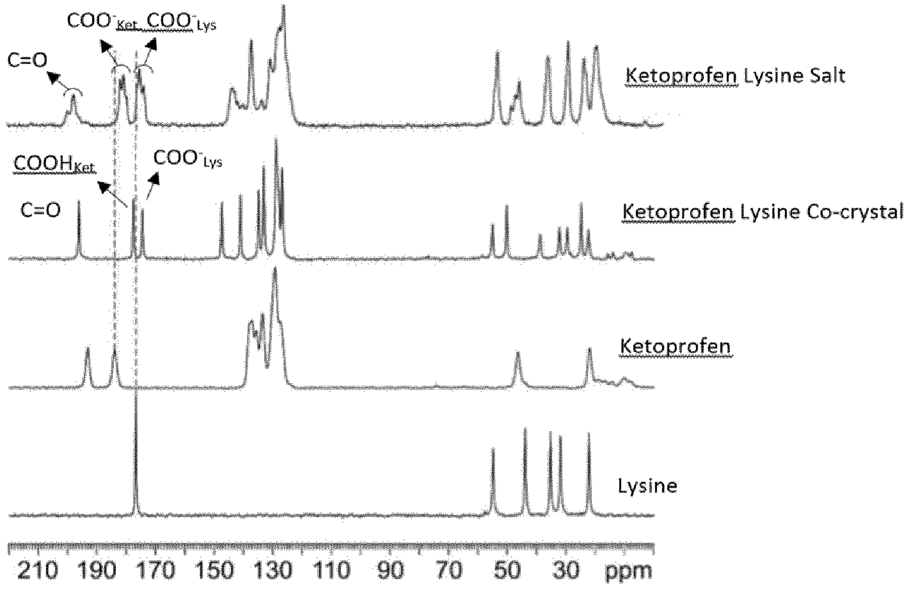
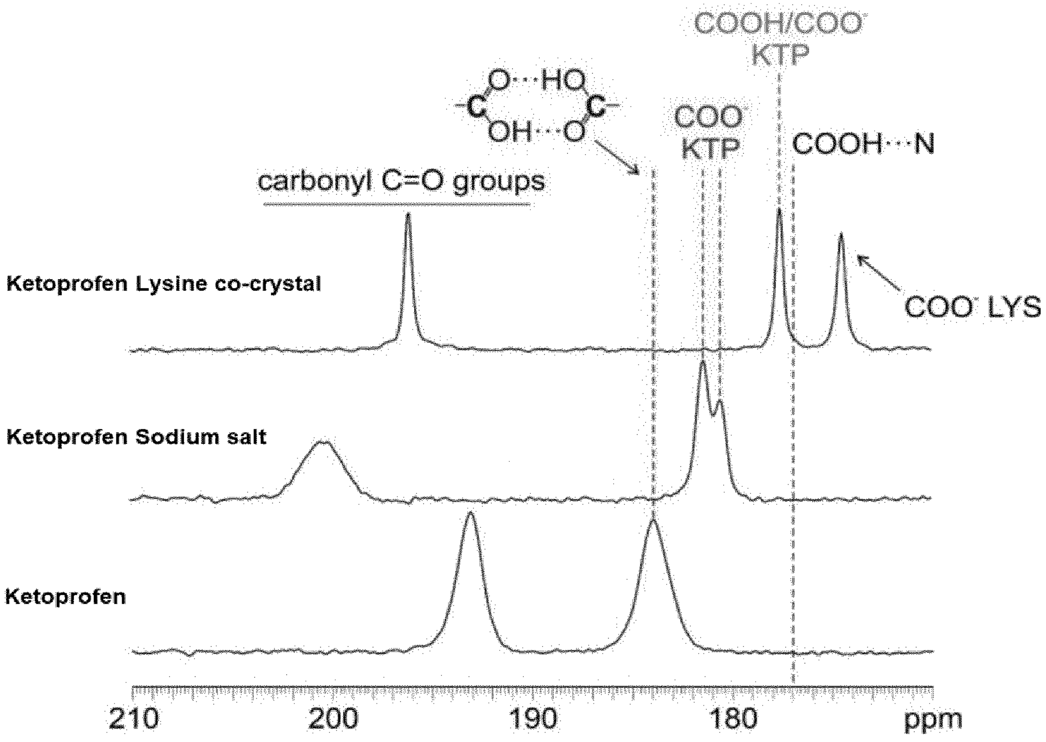
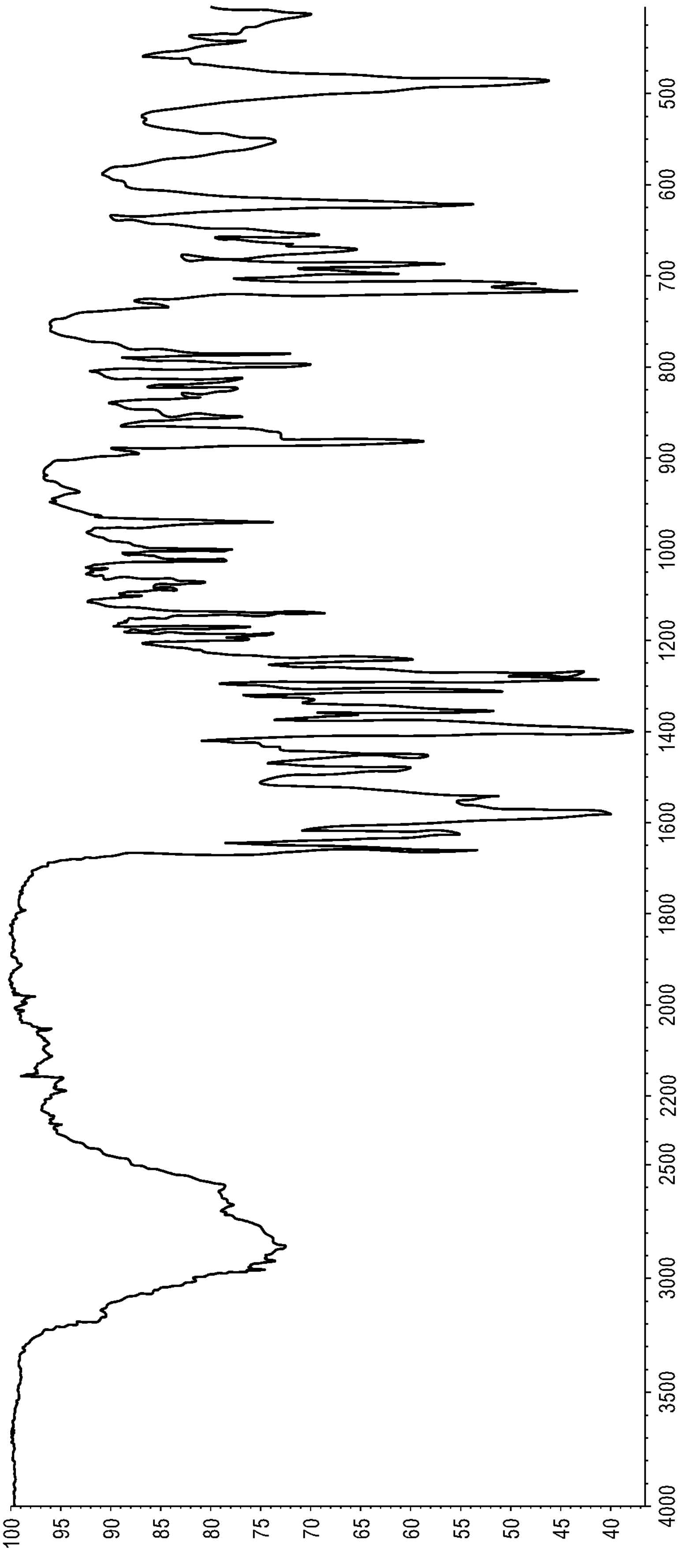


Figure 9


COOH/COO^-
KTP
COO
KTP
COOH···N
carbonyl C=O groups
Ketoprofen Lysine co-crystal
COO^- LYS
Ketoprofen Sodium salt
Ketoprofen
210
200
190
180
ppm


100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2200
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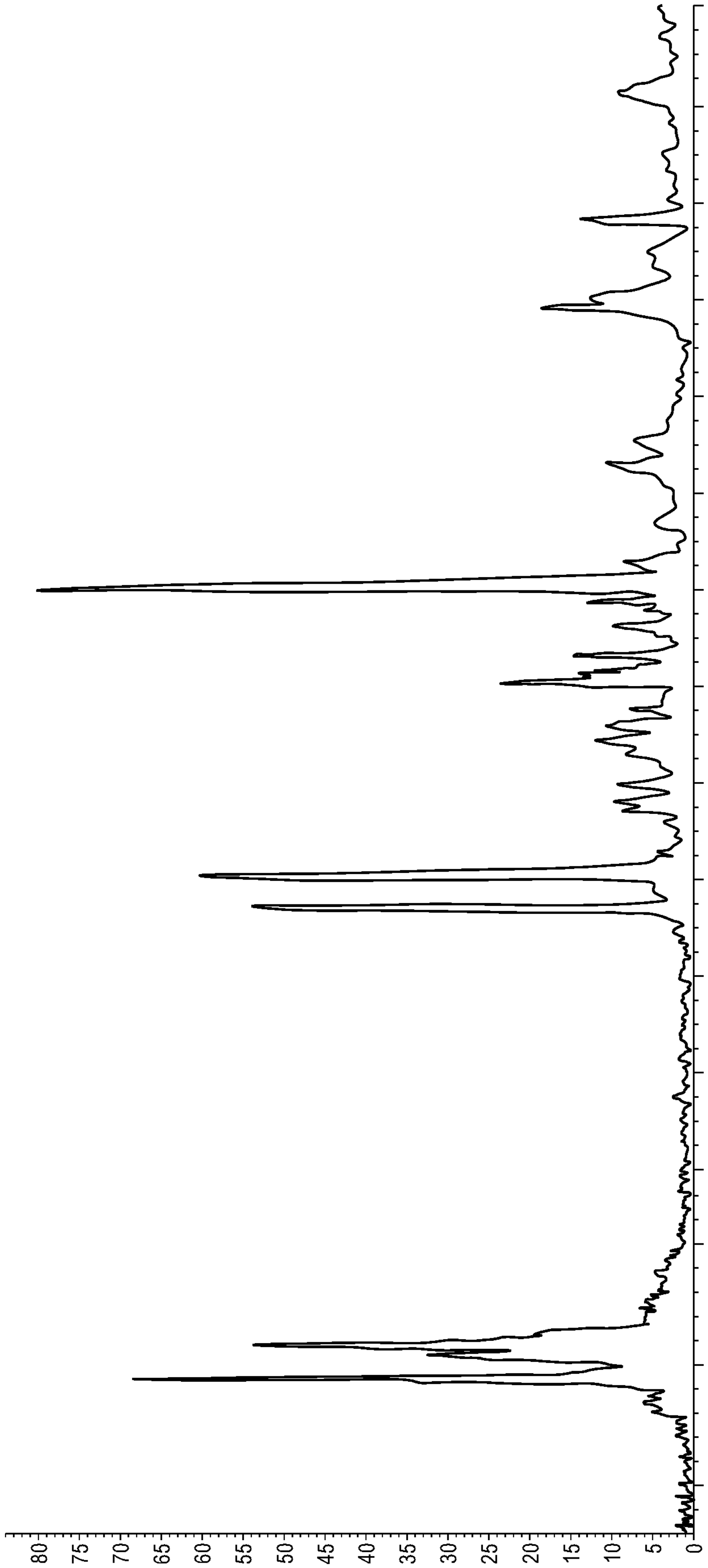
1800
1600
1400
1200
1000
900
800
700
600
500

FIG. 10


80
75
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45
40
35
30
25
20
15
10
5
0
3500
3000
2500
2200
2000
1800
1600
1400
1200
1000
900
800
700
600
400

FIG. 11

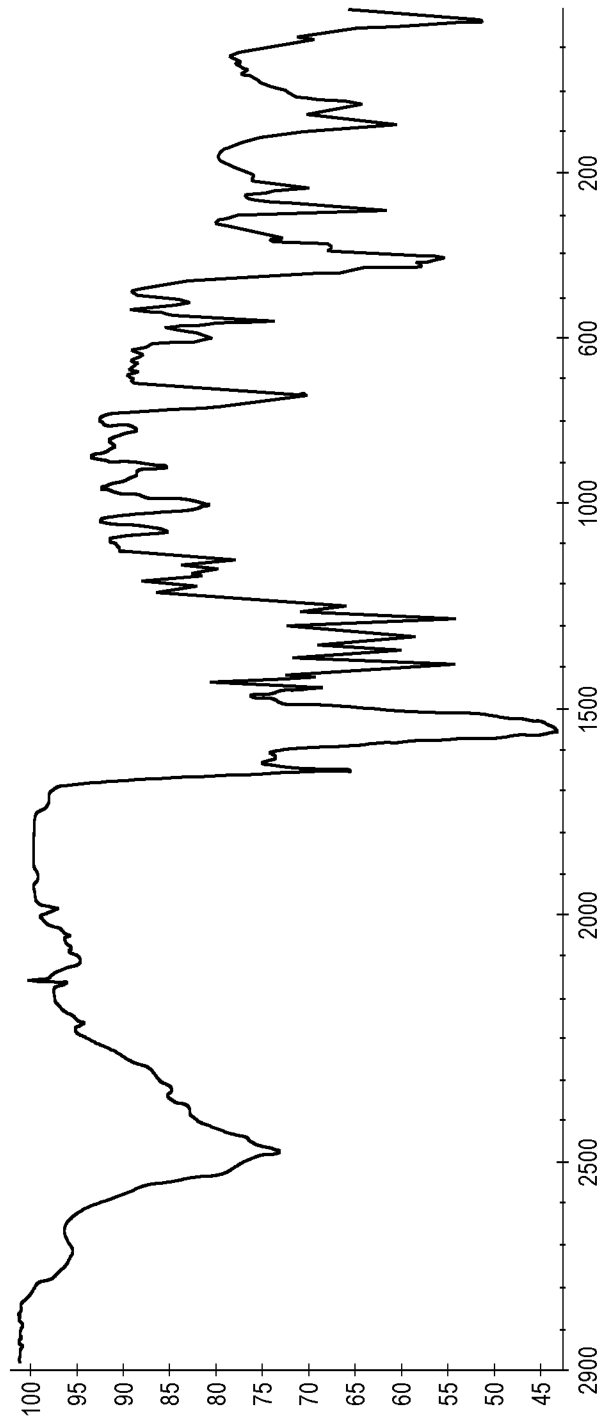

100
95
90
85
80
75
70
65
60
55
50
45
2900
2500
2000
1500
1000
600
200

FIG. 12

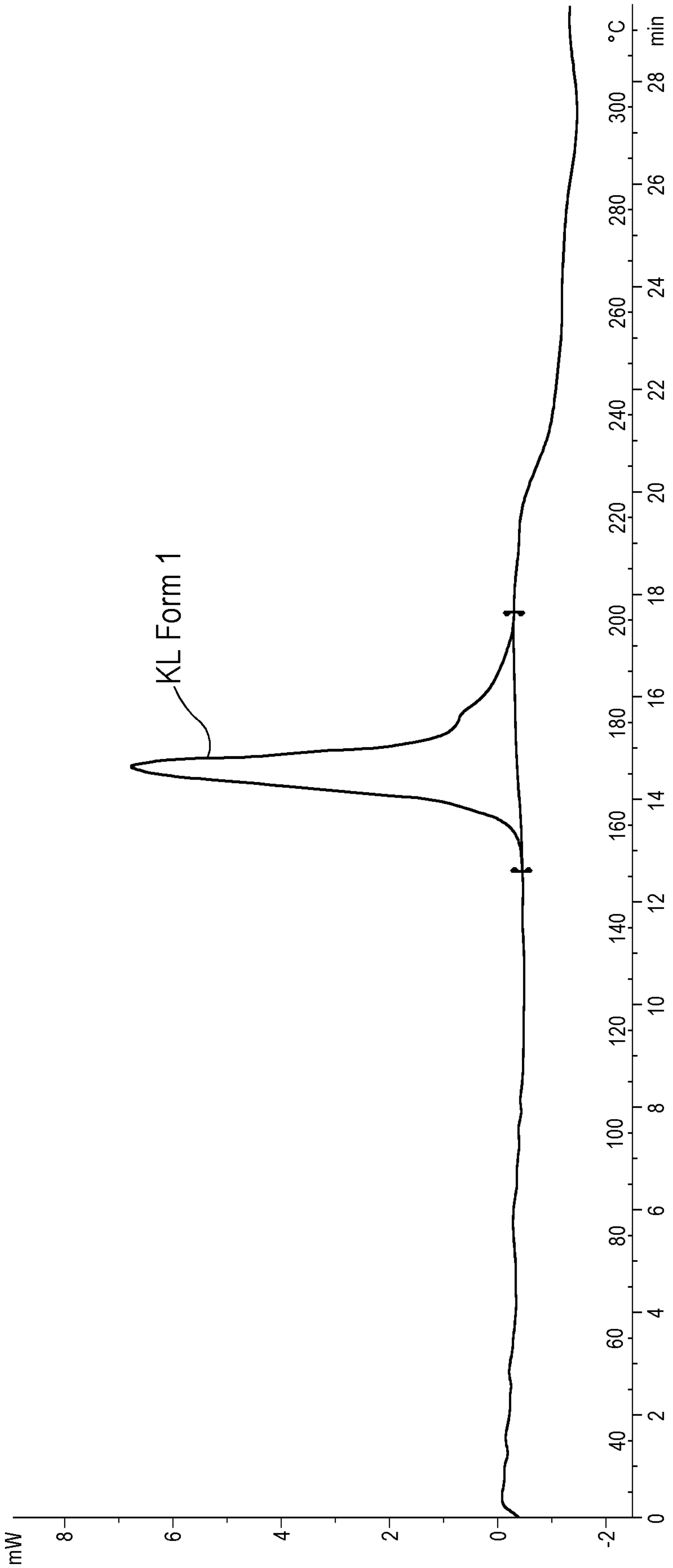

mW
8
6
4
2
0
-2
°C
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
min
2
4
6
8
10
12
14
16
18
20
22
24
26
28
KL Form 1

FIG. 13

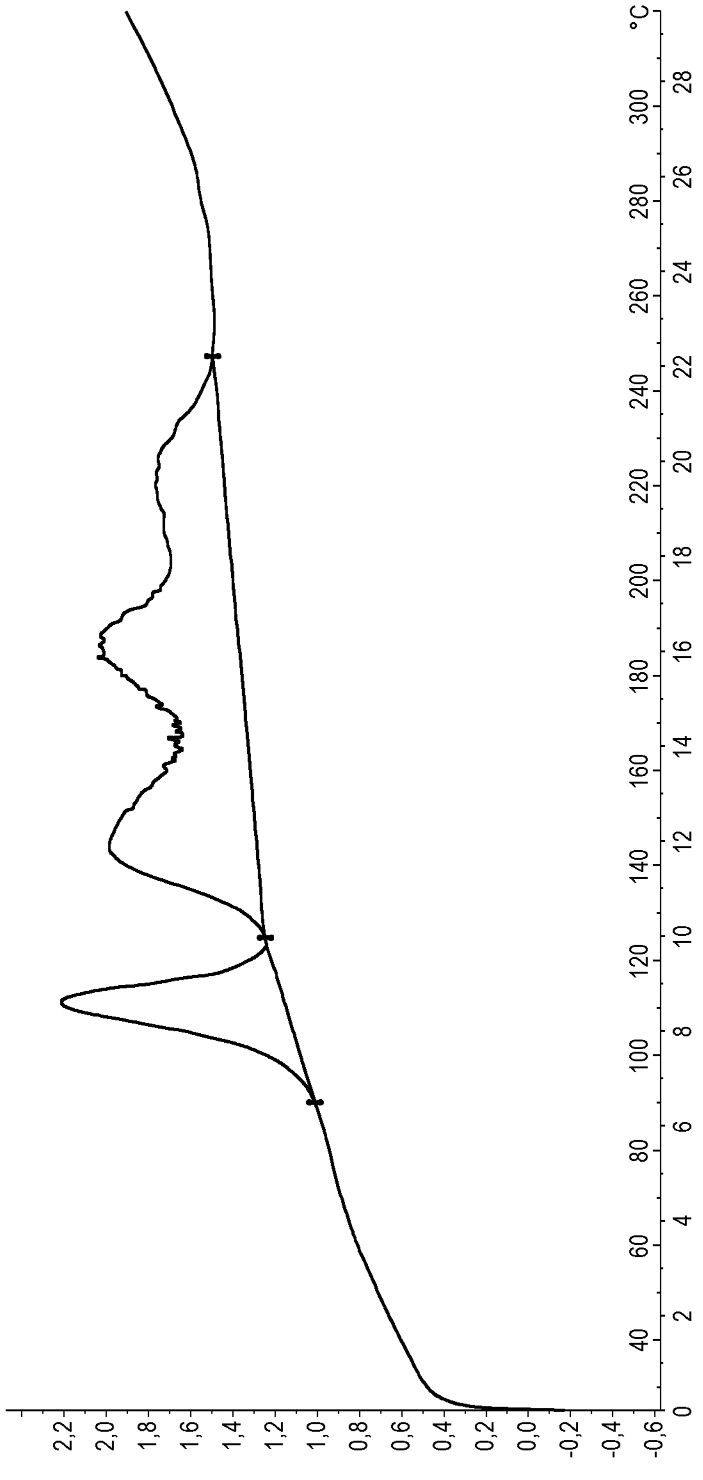

2,2
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
°C
2
4
6
8
10
12
14
16
18
20
22
24
26
28

FIG. 14

Figure 15

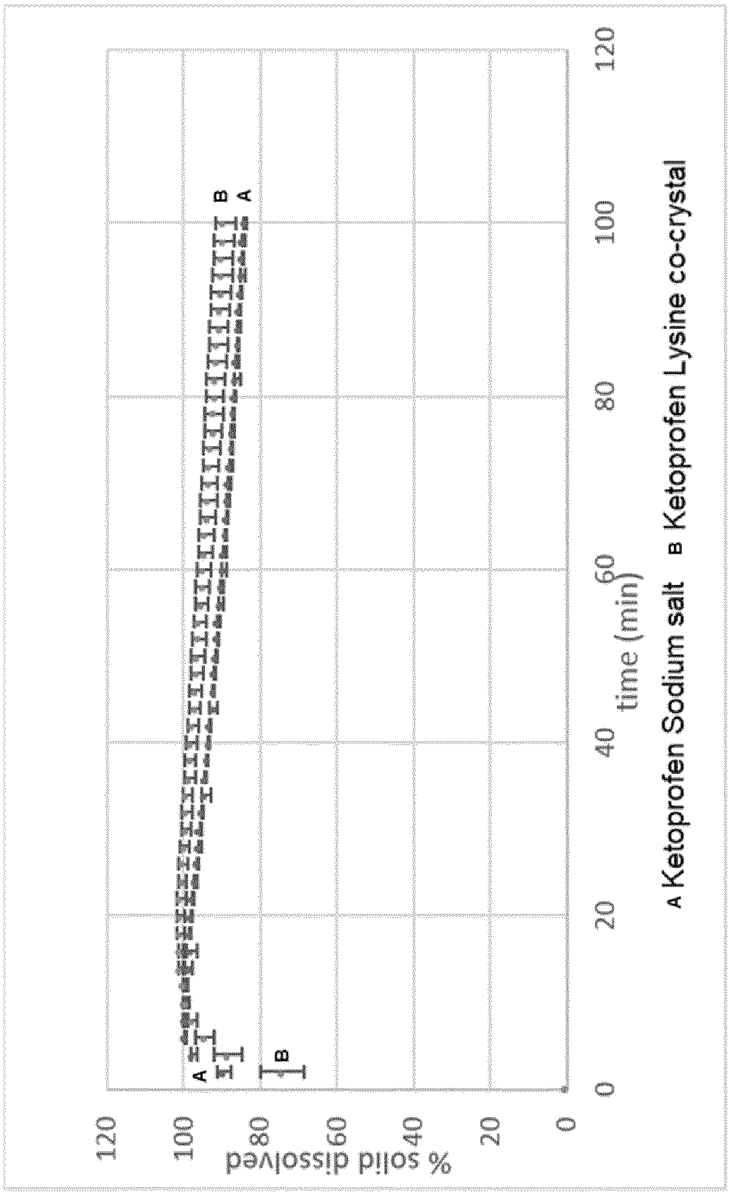

% solid dissolved
0
20
40
60
80
100
120
time (min)
0
20
40
60
80
100
120
A
B
A Ketoprofen Sodium salt
B Ketoprofen Lysine co-crystal

Figure 16

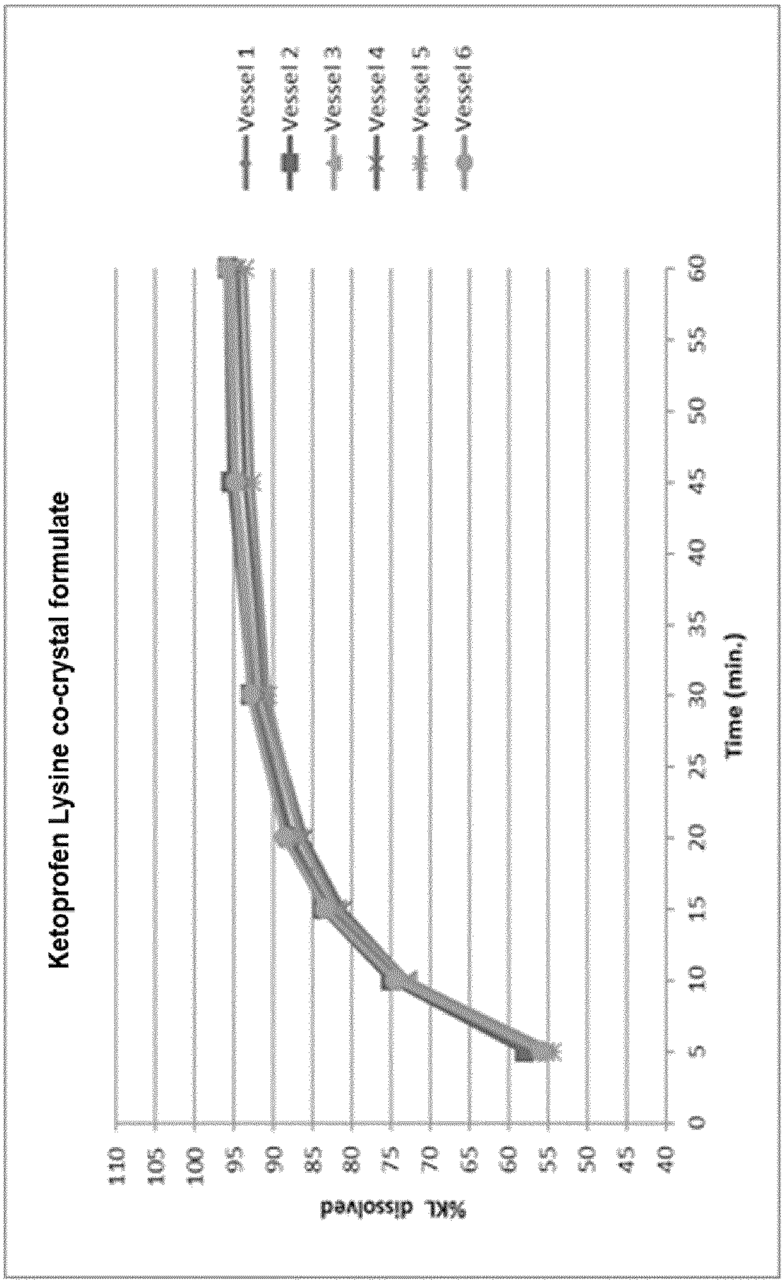
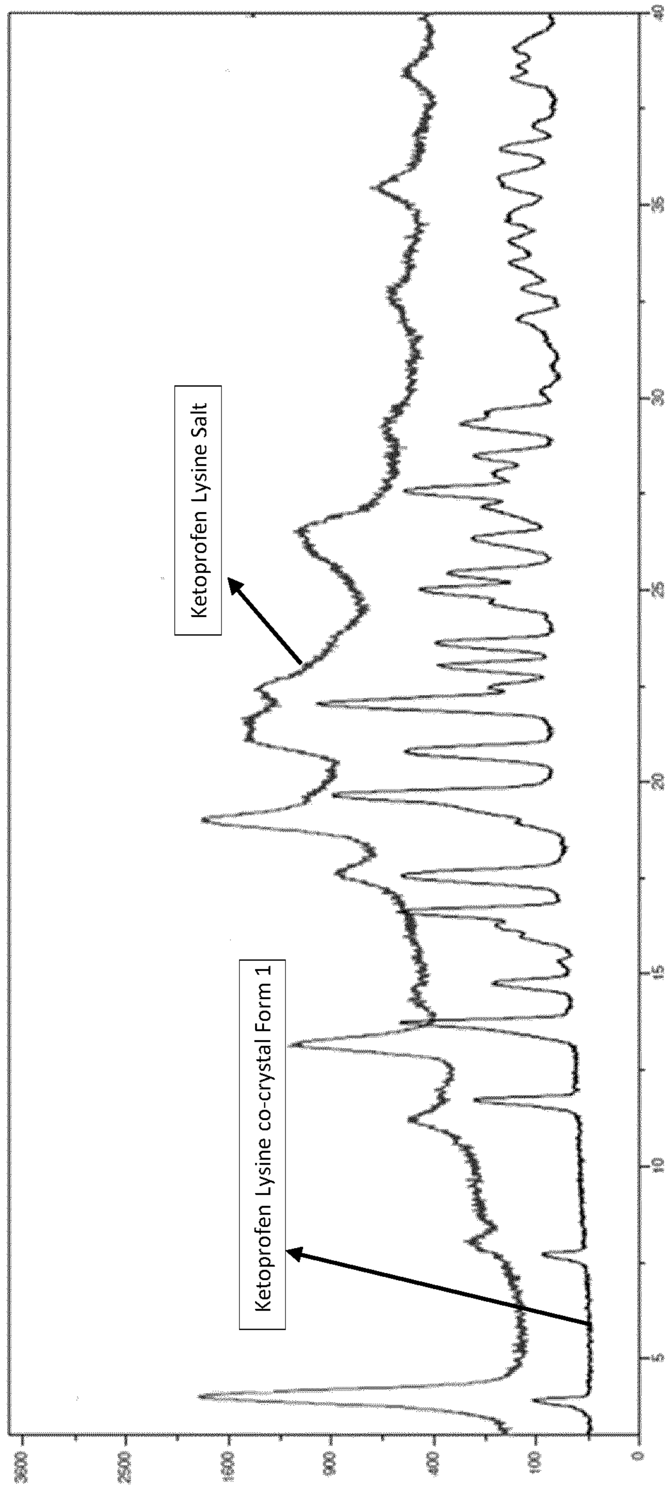

Ketoprofen Lysine co-crystal formulate
%KL dissolved
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
Time (min.)
0
5
10
15
20
25
30
35
40
45
50
55
60
Vessel 1
Vessel 2
Vessel 3
Vessel 4
Vessel 5
Vessel 6

Figure 17


Ketoprofen Lysine Salt
Ketoprofen Lysine co-crystal Form 1
3600
2500
1600
900
400
100
0
5
10
15
20
25
30
35
40

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/025464

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C51/41 C07C57/30 C07C59/84 C07C201/00 C07C231/24
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)
C07C

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 497 044 A (PRODOTTI ANTIBIOTICI SPA) 5 January 1978 (1978-01-05) examples 1,5 -----	1-20
X	BE 882 889 A (DOMPE FARMACEUTICI SPA) 18 August 1980 (1980-08-18) Example page 3 -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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 30 March 2020	Date of mailing of the international search report 08/04/2020
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Hacking, Michiel

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/025464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1497044 A	05-01-1978	AU 7880375 A	09-09-1976
		BE 826446 A	30-06-1975
		CA 1070324 A	22-01-1980
		DE 2508895 A1	18-09-1975
		ES 435416 A1	01-12-1976
		FR 2262975 A1	03-10-1975
		GB 1497044 A	05-01-1978
		JP S5912650 B2	24-03-1984
		JP S50126818 A	06-10-1975
		NL 7502644 A	09-09-1975
		US 4279926 A	21-07-1981
BE 882889 A	18-08-1980	BE 882889 A	18-08-1980
		IT 1104556 B	21-10-1985