Title: CO-CRYSTALS OF TRAMADOL AND COXIBS

Abstract: The present invention relates to co-crystals of tramadol and co-crystal formers selected from NSAIDs/coxibs, processes for preparation of the same and their uses as medicaments or in pharmaceutical formulations, more particularly for the treatment of pain. In a preferred embodiment, the co-crystal is (rac) - tramadol. HCl - celecoxib (1:1).
Co-crystals of Tramadol and Coxibs

The present invention relates to co-crystals of tramadol and NSAIDs – like coxibs –, processes for preparation of the same and their uses as medicaments or in pharmaceutical formulations, more particularly for the treatment of pain.

Pain is a complex response that has been functionally categorized into sensory, autonomic, motor, and affective components. The sensory aspect includes information about stimulus location and intensity while the adaptive component may be considered to be the activation of endogenous pain modulation and motor planning for escape responses. The affective component appears to include evaluation of pain unpleasantness and stimulus threat as well as negative emotions triggered by memory and context of the painful stimulus.

In general, pain conditions can be divided into chronic and acute. Chronic pain includes neuropathic pain and chronic inflammatory pain, for example arthritis, or pain of unknown origin, as fibromyalgia. Acute pain usually follows non-neural tissue injury, for example tissue damage from surgery or inflammation, or migraine.

There are many drugs that are known to be useful in the treatment or management of pain. Opioids are frequently used as analgesics in pain. Derivatives of morphine are indicated for the treatment of moderate to acute pain in human. The analgesic effect is obtained through their action on morphinic receptors, preferably the μ-receptors. Among these derivatives of morphine, may be mentioned morphine, codeine, pethidine, dextropropoxyphene, methadone, lenefopan and others.

One of the morphinic derivatives that has shown very good results when orally administrated, and which is extensively marketed, is Tramadol, also available as a physiologically acceptable salt, particularly as a chlorohydrate. Tramadol, whose chemical name is 2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol, has the following formula:
This structure shows two different chiral centers and thus may exist in different diastereoisomers among which the tramadol is the cis-diastereisomer: (1R, 2R), or (1S, 2S), both also known as (+)-tramadol and (-)-tramadol and both of which contribute in different ways to its activity.

From the art it appears that this compound is neither fully opioid-like, nor non-opioid-like. Some studies have demonstrate that tramadol is an opioid agonist, whereas clinical experience indicates that it lacks many of the typical side effects of opioids agonist, for example respiratory depression, constipation or tolerance.

Due to their drawbacks, opioids cannot always be given repeatedly or at higher doses as analgesics to treat pain. The side effects of opioids are known in the art including e.g. J. Jaffe in "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 8th edition; Gilman et al.; Pergamon Press, New York, 1990, Chapter 22, pages 522-573.

Consequently it has been proposed to combine opioids with other drugs that are not opioid analgesic agents, in order to lower the amount of opioids needed to produce an equivalent degree of analgesia. Among these combinations, the association of tramadol with nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported to be of particular interest (EP-0 546 676).

Thus it was the objective of the current invention to provide new means of improving the properties of tramadol, especially in regard to the treatment of pain, by providing new drugable forms of tramadol.

Especially desirable improvements/advantages of the new drugable form would include:

- improvement of physicochemical properties in order to facilitate the formulation, the manufacture, or to enhance the absorption and/or the bioavailability:
  - thus
  - being more active when compared to tramadol base or hydrochloride salt; or
  - providing a form of tramadol with a further active agent having a beneficial pharmacological effect in itself, thus allowing for a highly efficient dose/weight relation of the final active principle or even
  - allowing the use of a lower therapeutic dose of either tramadol and the further active agent, an NSAID – the coxib -, or of both;
  - having a synergistic effect through the combination of tramadol and the further active agent, an NSAID – the coxib -, in the same new drugable form; or
further
- having the bitter taste of tramadol removed or ameliorated;
- being easily obtainable, easy to manufacture or
- allowing more flexibility in formulating, or facilitating its formulation,
- being highly soluble, thus allowing better dissolution rates, especially if dissolving in an aqueous physiological surrounding, or
- improving stability of the co-crystal in comparison to the physical mixture of Tramadol/Active Agent (an NSAID – the coxib -) at the same ratio;
- allowing new routes of administration;
also
- allowing – if necessary - to combine tramadol with a chemically usually non-compatible active agent in the same formulation or even in immediate contact, without having to isolate tramadol;
or finally
- minimizing/reducing the side effects, especially the severe side effects, assigned to tramadol.

Other desirable improvements/advantages of the new drugable form would include being active in diseases or symptoms being or related to pain and its subtypes, especially those in which current treatment is insufficient like sciatica or frozen shoulder or pain related to central sensitization (central pain syndrome).

Most desirably the new drugable forms should combine more than one, most of these advantages.

This objective was achieved by providing new co-crystals of tramadol. It was found that tramadol was able to form co-crystals with NSAIDs – like coxib -, especially with celecoxib. These co-crystals show improved properties if compared to tramadol alone, and also good analgesic activity. The co-crystals thus obtained have a specific stoichiometry. Under the proper circumstance this is also another advantage of these new solid drugable forms possibly achieving some modulation of the pharmacological effects. While APIs (Active Pharmaceutical Ingredients) like tramadol in general have been recognized to form crystalline polymorphs, solvates, hydrates and amorphous forms for a number of years, there is little knowledge about which APIs will form co-crystals. Co-crystals are a specific type of crystalline form which provide a new avenue to modulate the API form and thus to modulate API properties. Co-crystals contain an API and at least one other component which crystallize together. Selection of the other component helps determine whether a co-crystal
will form and what properties the co-crystal will have. Just as a polymorph, solvate, hydrate or amorphous form of an API can modulate stability, solubility, and hygroscopicity, a co-crystal can modulate those same properties.

Thus the main object of the present invention is a co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one NSAID/coxib.

The coxibs are highly interesting NSAIDs for being the co-crystal former with tramadol. They are selective COX-2 inhibitors. The most important of these is the marketed drug celecoxib. Its chemical name is \(4-[5-(4-	ext{methylphenyl})-3-(\text{trifluoromethyl})-\text{pyrazol-1-yl}]\text{benzenesulfonamide}.\) It has an empirical formula of \(C_{17}H_{14}F_{3}N_{3}O_{2}S.\)

\[\text{Celecoxib}\]

NSAIDs like the coxibs have analgesic activity in a number of pain symptoms. The basis of their activity is inhibition of cyclooxygenase (COX), one of the two activities of prostaglandine endoperoxide synthase (PGHS). It is a key enzyme in the prostaglandin pathway.

“Drugable form (of tramadol)” as used herein is defined as any form (salt, amorphous crystal, solution, dispersion, mixture etc,) that tramadol might take which still can be formulated into a pharmaceutical formulation usable as a medicament to treat a disease or a symptom, especially pain.

“Co-Crystal” as used herein is defined as a crystalline material comprising two or more compounds at ambient temperature (20 to 25°C, preferably 20°C), of which at least two are held together by weak interaction, wherein at least one of the compounds is a co-crystal former. Weak interaction is being defined as an interaction which is neither ionic nor covalent and includes for example: hydrogen bonds, van der Waals forces, and \(\pi-\pi\) interactions. Solvates of tramadol that do not further comprise a co-crystal former are not co-crystals according to the present invention. The co-crystals may however, include one or more
solvate molecules in the crystalline lattice. Just for the sake of clarity the distinction between crystalline salt and a co-crystal has to be stressed here. An API bound to another compound forming a salt by means of ionic interaction can be considered as one "compound" according to the invention, but it cannot be considered as two compounds by itself.

In scientific literature there currently is some discussion on the proper use of the word co-crystal (see for example Desiraju, *Cryst. Eng. Comm.*, 2003, 5(82), 466-467 and Dunitz, *Cryst. Eng. Comm.*, 2003, 5(91), 506). A recent article by Zwarotko (Zwarotko, *Crystal Growth & Design*, Vol. 7, No. 1, 2007, 4-9) gives a definition of co-crystal which is in line with the definition given above and thus also is a definition of "co-crystal" according to this invention. According to this article "a co-crystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components consist of a target molecule or ion and a molecular co-crystal former(s); when in a co-crystal, they coexist at a molecular level within a single crystal".

"Co-crystal former" as used herein is defined as a molecule being an active agent selected from NSAIDs/Coxibs, and with which tramadol is able to form co-crystals.

"Active agents" are APIs which show a pharmaceutical effect and thus can be identified as being pharmacologically active. In a more narrow sense this definition is encompassing all APIs being marketed or under clinical trial for the treatment of diseases. "Active agents with analgesic activity" are APIs (Active Pharmaceutical Ingredients) which show efficacy in well-known animal models of pain and thus can be identified as being analgesics. In a more narrow sense this definition is encompassing all APIs being marketed or under clinical trial for a labelling including an indication falling under the definition of pain, including also migraine. These indications might include acute pain, chronic pain, neuropathic pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy, osteoarthritis or fibromyalgia and all their subforms. Examples of "active agents with analgesic activity" include an NSAID like celecoxib or tramadol and its N-desmethyl-metabolite.

"Pain" is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Even though pain is always subjective its causes or syndromes can be classified. One classification to denominate subtypes of pain would be to divide the general pain syndrome into the subtypes of acute and chronic pain or – according
to the pain intensity - into mild, moderate and severe pain. In other definitions the general pain syndrome is also divided into "nociceptive" (caused by activation of nociceptors), "neuropathic" (caused by damage to or malfunction of the nervous system) and pain related to central sensitization (central pain syndrome).

According to the IASP "alldynia" is defined as "a pain due to a stimulus which does not normally provoke pain" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 210). Even though the symptoms of alldynia are most likely associated as symptoms of neuropathic pain this is not necessarily the case so that there are symptoms of alldynia not connected to neuropathic pain though rendering alldynia in some areas broader than neuropathic pain.

The IASP further draws the following difference between "alldynia", "hyperalgesia" and "hyperpathia" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 212):

<table>
<thead>
<tr>
<th>Allodynia</th>
<th>Lowered threshold</th>
<th>Stimulus and response mode differ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperalgesia</td>
<td>Increased response</td>
<td>Stimulus and response rate are the same</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>Raised threshold; Increased response</td>
<td>Stimulus and response rate may be the same or different</td>
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According to the IASP "neuropathy" is defined as "a primary lesion or dysfunction in the nervous system" (IASP, Classification of chronic pain, 2nd Edition, IASP Press (2002), 211). Neuropathic pain may have central or peripheral origin.

"Sciatica" or "sciatic neuritis is defined herein as a set of symptoms including pain that derive from irritation of the sciatic nerve or its roots,

"Frozen shoulder" or "adhesive capsulitis" is defined herein as a symptom wherein the connective tissue surrounding the shoulder joint or the shoulder capsule itself, is causing chronic pain, becoming inflamed and stiff.

"Ankylosing spondylitis" or "Morbus Bechterew" is a chronic, inflammatory arthritis and autoimmune disease. It mainly affects joints in the spine and the sacroilium in the pelvis, causing eventual fusion of the spine.
“Pain related to central sensitization” / “central pain syndrome” is defined within this application as a neurological condition caused by damage to or dysfunction of the central nervous system (CNS), which includes the brain, brainstem, and spinal cord. This syndrome can _inter alia_ be caused by stroke, multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, or Parkinson's disease.

“Nociceptive pain ” is defined as a type of pain caused by activation of nociceptors. It can be divided into somatic and visceral pain. “Visceral pain” is pain generally originating from the organs, whereas “(deep) somatic pain” originates from ligaments, tendons, bones, blood vessels, fasciae and muscles.

In one embodiment of the co-crystal according to the invention, the NSAID/s / coxib/s is/are chosen in such a way that if compared to either tramadol alone, or to a mixture of tramadol and the corresponding active agent/s/ coxib:

- the solubility of the co-crystal is increased; and/or
- the dose response of the co-crystal is increased; and/or
- the efficacy of the co-crystal is increased; and/or
- the dissolution of the co-crystal is increased; and/or
- the bioavailability of the co-crystal is increased; and/or
- the stability of the co-crystal is increased; and/or
- the hygroscopicity of the co-crystal is decreased; and/or
- the form diversity of the co-crystal is decreased; and/or
- the morphology of the co-crystal is modulated.

“Mixture of tramadol and the corresponding active agent/s” is defined as a mixture of the active agent or agents in question (the NSAID/coxib) with tramadol which is only a physical mixture without any coupling forces between the compounds and thus neither includes salts nor another co-crystal.

In a further embodiment the NSAID being a Coxib is selected from celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, and cimicoxib.

In a further embodiment of the co-crystal according to the invention, the NSAID being a coxib is selected from:

- Celecoxib,
- Etoricoxib,
- Lumiracoxib,
- Parecoxib,
- Rofecoxib,
- Valdecoxib, or
- Cimicoxib.

Another very preferred aspect of the invention relates to a co-crystal according to the invention, wherein the NSAID being a coxib is celecoxib or salts thereof.

Another embodiment of the invention relates to a co-crystal according to the invention, wherein the tramadol is (-)-tramadol or (+)-tramadol or salt thereof.

Another embodiment of the invention relates to a co-crystal according to the invention, wherein the tramadol is (rac)-tramadol or salt thereof.

Especially preferred is a pharmaceutical compound comprising tramadol and celecoxib, preferably a pharmaceutical compound comprising (rac)-tramadol·HCl and celecoxib.

As illustrated in more detail below tramadol - and especially the racemate - forms co-crystals with celecoxib. Generally co-crystals obtained have a specific stoichiometry which depends upon the structure of each co-crystal forming NSAID. In this specific case of the co-crystal between (rac)-tramadol and celecoxib being the co-crystal former the molecular ratio between tramadol and celecoxib is 1 to 1.

The term “salt” is to be understood as meaning any form of tramadol or the NSAID/coxib according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of tramadol or the NSAID/coxib with other molecules and ions, in particular complexes which are complexed via ionic interactions. This also includes physiologically acceptable salt.

The term “solvate” according to this invention is to be understood as meaning any form of the tramadol or NSAID/coxib in which the compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcohol solvates, e.g. methanol solvate.

In a further preferred embodiment of the invention, co-crystal according to the invention, is selected from
• a co-crystal comprising (rac)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;
• a co-crystal comprising (+)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;
• a co-crystal comprising (-)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib; or preferably
• a co-crystal comprising (rac)-tramadol-HCl (the hydrochloride salt of tramadol) and celecoxib.

A highly preferred embodiment of the co-crystals according to the invention the co-crystal is formed from (rac)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib and celecoxib, preferably from (rac)-tramadol-HCl and celecoxib.

In a highly preferred embodiment of these selected co-crystals, the molecular ratio between the (rac)-tramadol-HCl and celecoxib is 1:1.

In a preferred embodiment of a co-crystal with a molecular ratio between (rac)-tramadol-HCl and celecoxib of 1:1 according to the invention, the co-crystal shows a Powder X-Ray Diffraction pattern with peaks [2θ] at 7.1, 9.3, 10.2, 10.7, 13.6, 13.9, 14.1, 15.5, 16.1, 16.2, 16.8, 17.5, 18.0, 19.0, 19.5, 19.9, 20.5, 21.2, 21.3, 21.4, 21.8, 22.1, 22.6, 22.7, 23.6, 24.1, 24.4, 25.2, 26.1, 26.6, 26.8, 27.4, 27.9, 28.1, 29.1, 29.9, 30.1, 31.1, 31.3, 31.7, 32.5, 32.8, 34.4, 35.0, 35.8, 36.2 and 37.2 [°].

The 2θ values were obtained using copper radiation (Cu_Kα 1.54060Å).

In a preferred embodiment of a co-crystal with a molecular ratio between (rac)-tramadol-HCl and celecoxib of 1:1 according to the invention, the co-crystal shows a Fourier Transform Infra Red pattern with absorption bands at 3481.6 (m), 3133.5 (m), 2923.0 (m), 2667.7 (m), 1596.0 (m), 1472.4 (m), 1458.0 (m), 1335.1 (m), 1288.7 (m), 1271.8 (m), 1168.7 (s), 1237.3 (m), 1168.7 (s), 1122.6 (s), 1100.9 (m), 1042.2 (m), 976.8 (m), 844.6 (m), 820.1 (m), 786.5 (m) 625.9 (m) cm⁻¹.

In a preferred embodiment of a co-crystal with a molecular ratio between (rac)-tramadol-HCl and celecoxib of 1:1 according to the invention, the co-crystal has an orthorhombic unit cell with the following dimensions:

\[ a = 11.0323(7) \text{ Å} \]
\[ b = 18.1095(12) \text{ Å} \]
c = 17.3206(12) Å

In a preferred embodiment of a co-crystal with a molecular ratio between (rac)-tramadol-HCl and celecoxib of 1:1 according to the invention, the endothermic sharp peak of the co-crystal corresponding to the melting point has an onset at 164 °C.

Another embodiment of the present invention relates to a process for the production of a co-crystal according to the invention as described above comprising the steps of:

(a) dissolving or suspending an NSAID - like a coxib - in a solvent; optionally heating the solution or dispersion to a temperature above ambient temperature and below the boiling point of the solution or dispersion;
(b) dissolving together with, or after, or before step (a) tramadol either as a free base or as a salt in a solvent,
(c) adding the solution of (b) to the solution of (a) and mixing them;
(d) cooling the mixed solution/dispersion of step (c) to ambient temperature;
(e) optionally evaporating part or all of the solvent; and
(f) filtering-off the resulting co-crystals.

Another embodiment of the present invention relates to a process for the production of a co-crystal according to the invention as described above comprising the steps of:

(a) dissolving or suspending an NSAID - like a coxib - in a solvent; optionally heating the solution or dispersion to a temperature above ambient temperature and below the boiling point of the solution or dispersion;
(b) dissolving together with, or after, or before step (a) tramadol either as a free base or as a salt in a solvent, optionally combined with step (a) by dissolving tramadol already together with the NSAID - like a coxib - in step (a)
(c) optionally adding the solution of (b) to the solution of (a) and mixing them;
(d) optionally adding a solvent to the solution of (a), (b) or (c) and mixing them;
(e) cooling the mixed solution/dispersion of step (a), (b), (c) or (d) to ambient temperature or below;
(f) optionally evaporating part or all of the solvent; and
(g) filtering-off the resulting co-crystals.

"Ambient temperature" is defined here as a temperature between 20 and 25°C, preferably being 20°C.
The solvents usable in these processes include water or organic solvents, preferably solvents selected from acetone, isobutyl acetate, acetonitrile, ethyl acetate, 2-butanol, dimethylcarbonate, chlorobenzene, butylether, diisopropylether, dimethylformamide, ethanol, water, hexane (also cyclohexane), isopropanol, methyl ethyl ketone (also methyl isobutyl-ketone), methanol, methyl t-butyl ether, 3-pentanone, toluene and 1,1,1-trichloroethane, most preferably including alcohols, like ethanol. It is preferable - but not necessary - that the solvents in steps (a) and (c) are identical.

The molecular ratio between tramadol and the NSAID – like the coxib - lies between 4:1 to 1:4, preferably from 3:1 to 1:3 and more preferably from 1:1 to 1:2.

Preferably the tramadol-solution in step (b) has a concentration of between 3M and 0.01 M.

The parts of the co-crystal according to the invention are well-known drugs with analgesic properties sometimes used for a long time worldwide. Due to this a further object of the present invention is a medicament comprising a co-crystal according to the invention.

Thus the invention also concerns a medicament comprising at least one co-crystal according to the invention as described above and optionally one or more pharmaceutically acceptable excipients.

The invention also relates to a pharmaceutical composition that comprises a therapeutically effective amount of the co-crystal according to the invention in a physiologically acceptable medium.

The association of two active principles in the same crystal exhibits several advantages. Being linked, they often behave as a single chemical entity, thus facilitating the treatments, formulation, dosage etc. In addition to that, with both tramadol and the NSAID – like the coxib - being active analgesics these co-crystals are highly useful in the treatment of pain, especially also not losing any activity/weight by the addition of pharmacologically useless counterions as in salts with no API. In addition the two active principles are complementing each other in the treatment especially of pain, but possibly also of various other diseases or symptoms. Thus, the co-crystals according to the invention do combine a high number of advantages over the state of the art.
Another advantage is that the association of two active principles into one unique species seems to allow for a better Pharmacokinetic/Pharmacodynamic (PKPD) including also a better penetration of the blood-brain barrier, which helps in the treatment of pain.

In general, in most embodiments in which the co-crystals of tramadol are used (e.g. for the treatment of pain etc.), these co-crystals would be formulated into a convenient pharmaceutical formulation or a medicament. Accordingly, a desirable advantage of a co-crystal of tramadol would show improved pharmaceutical properties and features, especially when compared to the free base or tramadol hydrochloride. Thus, the co-crystal of tramadol according to the invention should desirably show at least one, preferably more, of the following features:

- to have a very small particle size, e.g. from 300 μm or lower; or
- to be and/or remain essentially free of agglomerates; or
- to be less or not very hygroscopic; or
- to help in formulating controlled release or immediate release formulations; or
- to have a high chemical stability; or
- if given to a patient
  - to decrease the inter- and intra-subject variability in blood levels; or
  - to show a good absorption rate (e.g. increases in plasma levels or AUC); or
  - to show a high maximum plasma concentration (e.g. $C_{\text{max}}$); or
  - to show decreased time to peak drug concentrations in plasma ($t_{\text{max}}$); or
  - to show changes in half life of the compound ($t_{1/2}$), in whichever direction this change is preferably directed.

The medicament or pharmaceutical compositions according to the present invention may be in any form suitable for the application to humans and/or animals, preferably humans including infants, children and adults and can be produced by standard procedures known to those skilled in the art. The medicament of the present invention may for example be administered parenterally, including intramuscular, intraperitoneal, or intravenous injection, transmucosal or sublingual application; or orally, including administration as tablets, pellets, granules, capsules, lozenges, aqueous or oily solutions, suspensions, emulsions, sprays or as reconstituted dry powdered form with a liquid medium.

Typically, the medicaments according to the present invention may contain 1-60 % by weight of one or more of the co-crystals as defined herein and 40-99 % by weight of one or more auxiliary substances (additives/exciipients).
The compositions of the present invention may also be administered topically or via a suppository.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans preferably is in the range of 5 to 500 milligrams of tramadol to be administered during one or several intakes per day.

A further aspect of the invention relates to the use of a co-crystal according to the invention as described above for the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy or osteoarthritis or fibromyalgia. The invention thus also relates to the use of a co-crystal according to the invention as described above in the production of a medicament for the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy or osteoarthritis or fibromyalgia. A further aspect of the invention relates to the use of a co-crystal according to the invention as described above for the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, severe to moderate pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy, osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. The invention thus also relates to the use of a co-crystal according to the invention as described above in the production of a medicament for the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, severe to moderate pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy, osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. A further aspect of the invention relates to a co-crystal according to the invention as described above for (use in) the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy or osteoarthritis or fibromyalgia. A further aspect of the invention relates to the co-crystal according to the invention as described above for (use in) the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, severe to moderate pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy, osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. Preferably these uses are provided for in form of a medicament or a pharmaceutical composition according to the invention as described above.

A further aspect of the invention relates to a co-crystal according to the invention as described above for (use in) the treatment of pain, or preferably acute pain, chronic pain (acute and chronic pain), neuropathic pain, nociceptive pain (visceral and/or somatic pain),
mild and severe to moderate pain, hyperalgesia, pain related to central sensitization, allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy and osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. A further aspect of the invention relates to the use of a co-crystal according to the invention as described above for the treatment of pain, preferably acute pain, or preferably acute pain, chronic pain (acute and chronic pain), neuropathic pain, nociceptive pain (visceral and/or somatic pain), mild and severe to moderate pain, hyperalgesia, pain related to central sensitization, allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy and osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. The invention thus also relates to the use of a co-crystal according to the invention as described above in the production of a medicament for the treatment of pain, preferably acute pain, chronic pain (acute and chronic pain), neuropathic pain, nociceptive pain (visceral and/or somatic pain), mild and severe to moderate pain, hyperalgesia, pain related to central sensitization, allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy and osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica. Preferably these uses are provided for in form of a medicament or a pharmaceutical composition according to the invention as described above.

The uses of a co-crystal according to the invention (described above) or the respective method of treatment (described below) is preferably related to pain, including nociceptive pain (which includes somatic and visceral pain). These preferred embodiments of the invention may also be related to neuropathic pain and/or to pain related to central sensitization (the so-called "central pain syndrome").

The uses of a co-crystal according to the invention (described above) or the respective method of treatment (described below) may preferably also be related to acute and chronic pain.

The uses of a co-crystal according to the invention (described above) or the respective method of treatment (described below) may preferably also be related to mild, to moderate and to severe pain.

Another object of the current invention is a method of treatment of pain, preferably acute pain, chronic pain, neuropathic pain, hyperalgesia, allodynia or cancer pain, including diabetic neuropathy or osteoarthritis or fibromyalgia, by providing to a patient in need thereof a sufficient amount of a co-crystal according to the invention as described above. Another
object of the current invention is a method of treatment of pain, preferably acute pain, chronic
pain (acute and chronic pain), neuropathic pain, nociceptive pain (visceral and/or somatic
pain), mild and severe to moderate pain, hyperalgesia, pain related to central sensitization,
allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy and
osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or
sciatica, by providing to a patient in need thereof a sufficient amount of a co-crystal
according to the invention as described above. Preferably the co-crystal according to the
invention is provided in physiologically suitable form like e.g. in form of a medicament or a
pharmaceutical composition according to the invention as described above.

The present invention is illustrated below with the help of the following figures and examples.
These illustrations are given solely by way of example and do not limit the invention.

**Brief description of the figures:**

**Figure 1:**
Powder X-Ray diffraction pattern of the (rac)-tramadol·HCl-celecoxib (1:1) co-crystal.

**Figure 2:**
DSC analysis of the (rac)-tramadol·HCl-celecoxib (1:1) co-crystal.

**Figure 3:**
TG analysis of the (rac)-tramadol·HCl-celecoxib (1:1) co-crystal.

**Figure 4:**
Structure of the unit cell of the (rac)-tramadol·HCl-celecoxib (1:1) co-crystal obtained by
SCXRD analysis showing two molecules of celecoxib and two molecules of tramadol.

**Figure 5:**
Showing bioavailability of a co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) in dogs
compared to celecoxib alone and to the combination of both API's (the mixture of tramadol
and celecoxib).

**Figure 6:**
Comparison of the effects of a co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), of tramadol
and of celecoxib on reversal of incision-induced mechanical allodynia in the incised rat hind
paw following a single dose (8–10 per group). All data are presented as means ± SEM.
**Figure 7:**
Isobologram showing anti-allodynic interaction of celecoxib (ED$_{50}$ = 3.01 mg/kg) and tramadol (ED$_{50}$ = 5.28 mg/kg) on mechanical allodynia in the paw incision postoperative pain model in rats. The oblique line between x- and y axis is the theoretical additive line. The point in the middle of this line is the theoretical additive point calculated from separate ED$_{50}$. Red: the experimental point (co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) ED$_{50}$, molecular weight ratio 1:1.27) lies far below the theoretical ED$_{50}$ (blue), indicating a significant (P <0.05) synergistic interaction.

**Figure 8:**
Comparison of the effects of a co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), of tramadol and of celecoxib on reversal of incision-induced thermal hyperalgesia in the incised rat hind paw following a single dose (8–10 per group). All data are presented as means ± SEM.

**Figure 9:**
Effects of a co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) [the right column in each triplet of bars], of tramadol [the central/middle column in each triplet of bars] and of celecoxib [the left column in each triplet of bars] given intraperitoneally 4.5 h after induction by carrageenan (n = 8-10 per dose group), on motor behaviour of monoarthritic rats measured walking across the CBMS 30 min after drugs administration.

**EXAMPLES**

**Example 1: (rac)-tramadol·HCl – celecoxib (1:1) co-crystal**

**Processes to obtain (rac)-tramadol·HCl – celecoxib (1:1) co-crystal:**

**Example 1a: (preparation via solvent-assisted grinding)**
A 5mL stainless steel ball-mill reactor was charged with two 7mm steel balls, (rac)-tramadol hydrochloride (48mg, 0.16mmol), celecoxib (61mg, 0.16mmol, 1eq) and 1 drop of methyl isobutyl ketone. The reactor was agitated at 30Hz for 45 minutes. Traces of solvent were removed in vacuo affording (rac)-tramadol·HCl – celecoxib (1:1) co-crystal as a white solid (109 mg, quantitative yield).

**Example 1b: (large scale via crystallization)**
To a 1 L three necked flask equipped with mechanical stirrer, addition funnel and cooler containing tramadol-HCl (26.54 g, 88.5 mmol) and celecoxib (33.74 g, 88.5 mmol, 1 eq.), was added 122 mL ethanol. The resultant suspension was heated to reflux (complete dissolution). Cyclohexane (203 mL) was added slowly to the solution maintaining the reflux (addition time 20 min) and then, the solution was cooled slowly to room temperature with stirring. The solution was seeded at 55° C with form obtained in Example 1a and the crystallization started. The mixture was cooled 2 h at 0° C. The white solid was filtered with a sintered funnel n° 3 and washed with a solvent mixture at 0-5° C (1 vol., 60 mL, (0.6:1) EtOH / cyclohexane). After drying 2 days at room temperature under vacuum, (rac)-tramadol-HCl – celecoxib (1:1) co-crystal was obtained as a white solid (54.6 g, 91 % yield).

**CHARACTERISATION OF THE CO-CRYSTAL:**
(rac)-Tramadol-HCl – celecoxib (1:1) co-crystal obtained according to example 1 was fully characterised by 1H-NMR, FTIR, powder X-Ray diffraction, DSC and TG (see figures 1 to 3).

**Powder X-ray diffraction (PXRD) pattern of a (rac)-tramadol-HCl – celecoxib (1:1) co-crystal:** (see Fig. 1):
PXRD analysis was performed using a Philips X’Pert diffractometer with Cu Kα radiation in Bragg-Brentano geometry. The system is equipped with a monodimensional, real time multiple strip detector. The measurement parameters were as follows: the range of 2θ was 3° to 40° at a scan rate of 8.8° per minute (see figure 1). The peaks expressed in angles 2θ and d-values are described in detail in table 1:

**Table 1: List of selected peaks obtained by powder X-Ray diffraction of (rac)-tramadol-HCl – celecoxib (1:1) co-crystal.**

<table>
<thead>
<tr>
<th>Angle 2θ</th>
<th>d-Value (Å)</th>
<th>Relative Intensity %</th>
<th>Angle 2θ</th>
<th>d-Value (Å)</th>
<th>Relative Intensity %</th>
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</thead>
<tbody>
<tr>
<td>7.06</td>
<td>12.52</td>
<td>29</td>
<td>23.57</td>
<td>3.78</td>
<td>15</td>
</tr>
<tr>
<td>9.32</td>
<td>9.49</td>
<td>1</td>
<td>24.11</td>
<td>3.69</td>
<td>13</td>
</tr>
<tr>
<td>10.21</td>
<td>8.67</td>
<td>5</td>
<td>24.36</td>
<td>3.65</td>
<td>10</td>
</tr>
<tr>
<td>10.69</td>
<td>8.27</td>
<td>2</td>
<td>25.20</td>
<td>3.53</td>
<td>6</td>
</tr>
<tr>
<td>13.64</td>
<td>6.49</td>
<td>10</td>
<td>26.12</td>
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<td>11</td>
</tr>
<tr>
<td>13.86</td>
<td>6.39</td>
<td>14</td>
<td>26.58</td>
<td>3.35</td>
<td>2</td>
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<tr>
<td>14.13</td>
<td>6.27</td>
<td>100</td>
<td>26.77</td>
<td>3.33</td>
<td>2</td>
</tr>
<tr>
<td>15.53</td>
<td>5.71</td>
<td>3</td>
<td>27.45</td>
<td>3.25</td>
<td>5</td>
</tr>
<tr>
<td>16.10</td>
<td>5.51</td>
<td>6</td>
<td>27.94</td>
<td>3.19</td>
<td>4</td>
</tr>
<tr>
<td>16.25</td>
<td>5.45</td>
<td>5</td>
<td>28.13</td>
<td>3.17</td>
<td>3</td>
</tr>
<tr>
<td>16.85</td>
<td>5.26</td>
<td>44</td>
<td>29.07</td>
<td>3.07</td>
<td>9</td>
</tr>
<tr>
<td>17.50</td>
<td>5.07</td>
<td>12</td>
<td>29.91</td>
<td>2.99</td>
<td>3</td>
</tr>
<tr>
<td>18.00</td>
<td>4.93</td>
<td>11</td>
<td>30.15</td>
<td>2.96</td>
<td>3</td>
</tr>
<tr>
<td>19.05</td>
<td>4.66</td>
<td>38</td>
<td>31.11</td>
<td>2.88</td>
<td>3</td>
</tr>
<tr>
<td>19.48</td>
<td>4.56</td>
<td>11</td>
<td>31.34</td>
<td>2.85</td>
<td>5</td>
</tr>
<tr>
<td>19.91</td>
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<td>31.74</td>
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<tr>
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<td>25</td>
<td>32.49</td>
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<td>3</td>
</tr>
<tr>
<td>21.18</td>
<td>4.19</td>
<td>11</td>
<td>32.83</td>
<td>2.73</td>
<td>2</td>
</tr>
<tr>
<td>21.27</td>
<td>4.18</td>
<td>11</td>
<td>34.42</td>
<td>2.61</td>
<td>1</td>
</tr>
<tr>
<td>21.44</td>
<td>4.14</td>
<td>8</td>
<td>35.04</td>
<td>2.56</td>
<td>2</td>
</tr>
<tr>
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<td>4.08</td>
<td>18</td>
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<td>2.51</td>
<td>1</td>
</tr>
<tr>
<td>22.14</td>
<td>4.02</td>
<td>3</td>
<td>36.24</td>
<td>2.48</td>
<td>2</td>
</tr>
<tr>
<td>22.56</td>
<td>3.94</td>
<td>14</td>
<td>37.19</td>
<td>2.42</td>
<td>1</td>
</tr>
<tr>
<td>22.73</td>
<td>3.91</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The 20 values were obtained using copper radiation (CuKα 1.54060 Å)*

'H-NMR spectrum of a co-crystal of (rac)-tramadol·HCl and celecoxib (1:1):'
Proton nuclear magnetic resonance analyses were recorded in methanol-\textit{d}_4 in a Varian Mercury 400 spectrometer, equipped with a broadband probe ATB 1H/19F/X of 5 mm. Spectra were acquired dissolving 5-10 mg of sample in 0.6 mL of deuterated solvent.

'\textsuperscript{1}H NMR spectrum (in d4-methanol at 400 MHz) \textit{δ} shows peaks at 7.97-7.90 (m, 2H); 7.53-7.46 (m, 2H); 7.30 (t, \textit{J} = 8.0 Hz, 1H); 7.22-7.14 (m, 4H); 7.12-7.09 (m, 1H); 7.07 (d, \textit{J} = 7.8 Hz, 1H); 6.90 (s, 1H); 6.83 (dd, \textit{J} = 2.7 Hz, \textit{J} = 8.2 Hz, 1H); 3.80 (s, 3H); 2.98 (dd, \textit{J} = 9.0 Hz, \textit{J} = 13.3 Hz, 1H); 2.75-2.60 (m, 8H); 2.35 (s, 3H); 2.28-2.18 (m, 1H); 2.00-1.46 (m, 8H) ppm.*

'FT-IR spectrum of a co-crystal of (rac)-tramadol·HCl and celecoxib (1:1):'
FTIR spectra were recorded using a Thermo Nicolet Nexus 870 FT-IR, equipped with a beamsplitter KBr system, a 35 mW He–Ne laser as the excitation source and a DTGS KBr detector. The spectra were acquired in 32 scans at a resolution of 4 cm\textsuperscript{-1}.

The sample (KBr pellet) shows a Fourier Transform Infra Red spectrum with absorption bands at 3481.6 (m), 3133.5 (m), 2923.0 (m), 2667.7 (m), 1596.0 (m), 1472.4 (m), 1458.0 (m), 1335.1 (m), 1288.7 (m), 1271.8 (m), 1168.7 (s), 1237.3 (m), 1168.7 (s), 1122.6 (s), 1100.9 (m), 1042.2 (m), 976.8 (m), 844.6 (m), 820.1 (m), 786.5 (m) 625.9 (m) cm\textsuperscript{-1}.

'DSC analysis of a co-crystal of (rac)-tramadol·HCl and celecoxib (1:1) (see Fig. 2):'
DSC analyses were recorded with a Mettler DSC822°. A sample of 1.6230 mg was weighed into 40 μL aluminium crucible with a pinhole lid and was heated, under nitrogen (50 mL/min), at 10°C/min from 30 to 200 °C.

The novel type of crystal of the present invention is characterized in that the endothermic sharp peak corresponding to the melting point has an onset at 164.44 °C (fusion enthalpy - 93.56 J/g), measured by DSC analysis (10 °C/min) (see figure 9).

**TG analysis of a co-crystal of (rac)-tramadol·HCl and celecoxib (1:1) (see Fig. 3):**
Thermogravimetric analyses were recorded in a thermogravimetric analyzer Mettler TGA/SDTA851°. A sample of 3.0560 mg was weighed into a 70 μL alumina crucible with a pinhole lid and was heated at 10 °C/min from 30 to 200 °C, under nitrogen (50 mL/min).

The TG analysis of the crystalline form according to the invention shows insignificant weight loss between 30 and 200 °C.

**Single Crystal XRD analysis of a single crystal of a co-crystal of (rac)-tramadol·HCl and celecoxib (1:1) (see Fig. 4):**
The crystal structure was determined from single crystal X-ray diffraction data. The colourless prism used (0.33 × 0.16 × 0.11 mm) was obtained from the crystallization of a seeded solution in heptane and IPA of equimolar amounts of (rac)-tramadol hydrochloride and celecoxib.
Analysis was performed at room temperature using a Bruker Smart Apex diffractometer with graphite monochromated Mo Kα radiation equipped with a CCD detector. Data were collected using phi and omega scans (program used: SMART 5.6). No significant decay of standard intensities was observed. Data reduction (Lorentz and polarization corrections) and absorption correction were applied (program used: SAINT 5.0).
The structure was solved with direct methods and least-squares refinement of $\mathbf{F}_o^2$ against all measured intensities was carried out (program used: SHELXTL-NT 6.1). All non-hydrogen atoms were refined with anisotropic displacement parameters. Crystal data and structure refinement for (rac)-tramadol-celecoxib (1:1) co-crystal is given in the following table 2.

**Table 2: Most relevant structural data of the SCXRD analysis of a co-crystal of (rac)-tramadol·HCl-celecoxib (1:1).**

<table>
<thead>
<tr>
<th>Crystal system</th>
<th>Orthorhombic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>Pna2₁</td>
</tr>
<tr>
<td>a (Å)</td>
<td>11.0323(7)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>18.1095(12)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>17.3206(12)</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Volume (Å³)</td>
<td>3460.5(4)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>D calc. (Mg/m³)</td>
<td>1.308</td>
</tr>
<tr>
<td>N. of refl.</td>
<td>8336</td>
</tr>
<tr>
<td>Refl. with l &gt; 2σ(l)</td>
<td>5240</td>
</tr>
<tr>
<td>R (l &gt; 2σ(l))</td>
<td>0.0584</td>
</tr>
</tbody>
</table>

The crystal structure is depicted in figure 4 (only half of the unitcell contents is shown; hydrogen atoms have been omitted for clarity; program used: Mercury 2.2, C.F. Macrae, I.J. Bruno, J.A. Chisholm, P.R. Edginton, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P.A. Wood, J. Appl. Cryst., 41, 2008, 466-470).

Simulation of XRPD diffractogram from single crystal data gives an almost identical diagram to the experimental one presented above.

**Example 1c: Determination of the bioavailability of co-crystal of (rac)-tramadol-HCl - celecoxib (1:1) (dogs)**

The objective was to measure plasma exposure of (rac)-tramadol-HCl and celecoxib in dogs by means of AUC determination of the co-crystal of (rac)-tramadol-HCl - celecoxib (1:1) of the present invention, and comparing it with each active principle of the co-crystal and the fixed combination of the two active principles.

Bioavailability of (rac)-tramadol-HCl-celecoxib co-crystal was compared to those obtained after administration of (rac)-tramadol-HCl plus celecoxib, combined and separately, to beagle dogs (3 males and 3 females) by oral route. Products with an equivalent particle size were orally administered by means of capsules at a dose level of 10 mg/kg of co-crystal (as base) and at an equivalent dose level of comparators (4.1 mg tramadol/kg, 5.9 mg celecoxib/kg). Blood from the dogs was extracted at the following time points: predose, 15 and 30 min; 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8 and 24h. The plasma was isolated by centrifugation, purified by SPE and plasma levels were determined by LC-MS-MS. Pharmacokinetic parameters were calculated using non-compartmental pharmacokinetic analysis.

The results showed an increase exposure of celecoxib when the co-crystal (rac)-tramadol-HCl - celecoxib was administered compared to celecoxib alone and to the combination of both API's (the mixture of tramadol and celecoxib) (see Fig. 5).
Example 1d: Effects on Mechanical Allodynia and Thermal Hyperalgesia in a Postoperative Pain Model in Rat

The aim of this study was to evaluate the analgesic efficacy and potency of co-crystal of (rac)-tramadol-HCl - celecoxib (1:1), tramadol and celecoxib in a rat model of postoperative pain after paw incision. Following plantar incision, rats show decreases in response thresholds to temperature (thermal hypersensitivity) and graded von Frey filaments (mechanical hypersensitivity) (Brennan et al., Pain 1996, 64, 493).

To assess the reliability of the efficacy and potency of the compounds tested, two different behavioural assays have been used: tactile allodynia using up and down paradigm by von Frey filaments and thermal hyperalgesia using the plantar test assay (Hargreaves et al., Pain 1988, 32, 77).

Experimental design:

Animals

Male, Wistar rats (120–160 g, Harlan, Italy) were housed in a climate-controlled room for at least 5 days prior to testing. Food and water were available ad libitum up to test time.

Animal Dosing

The rats were all dosed intraperitoneally with co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) or each agent separately, dissolved in a suspension of 0.5% hydroxypropyl methylcellulose in distilled water. The dosing volume was 10 ml/kg. The antihyperalgesic or antiallodynic response of the animal was subsequently evaluated 60 min after drug administration.

Surgery

Rats were anaesthetized with 3% isoflurane for veterinary use, employing an Ohmeda vaporizer and an anaesthesia chamber. Anaesthesia was kept during the surgical operation by a tube which directs the isoflurane vapours to the animal’s snout. Once the rats were anaesthetised, they were laid down in a prone position and their right hindpaws were cleaned out with alcohol. Then, a 1 cm longitudinal incision was made with a number 23 scalpel, through skin and fascia of the plantar aspect of the paw, starting 0.5 cm from the proximal edge of the heel and extending toward the toes. Therefore, both superficial (skin) and deep (muscle) tissues and nerves were injured. Finally, the skin of the paw was stitched with a suturing stitch with breaded silk (3.0) and the wound was cleaned out with povidone.

Assessment of analgesic activity in post-operative pain in rats
The drugs were tested 4 hours after the surgery (plantar incision); 60 minutes after the administration of the product, two behavioural endpoints were evaluated: thermal hypersensitivity or hyperalgesia, and mechanical hypersensitivity or allodynia.

Assessment of thermal hypersensitivity (hyperalgesia) in post-operative pain in rats
Hypersensitivity or hyperalgesia was assessed by measurement of a response to a thermal stimulus using a Hargreaves apparatus (Ugo Basile plantar test) which selectively elevates the temperature of an individual paw (Dirig, et al., J Neurosci Methods, 1997, 76, 183). Animals were placed in the methacrylate cages of said apparatus, having a crystal floor. The acclimation period within the cages was about 10 minutes. The thermal stimulus came from a lamp moving below the crystal floor and which was applied to both paws, with a minimum interval of 1 minute between both stimulations in order to avoid learning behaviours. The rat is able to withdraw the paw freely when it feels discomfort (pain) produced by the heat coming from the lamp; then it is switched off and the latency time to the withdrawal response is recorded in seconds. In order to avoid hurting the animal’s paw, the lamp was automatically switched off after 32 seconds. Hyperalgesia is defined as a reduced latency to response compared to the latency of a vehicle-treated animal, and the analgesic effect of the test compound is seen as a (partial) restoration of the latency toward normal (Dirig, et al., J. Pharmacol Expt Therap. 1998, 285, 1031).

Assessment of mechanical hypersensitivity (allodynia) in post-operative pain in rats
Mechanical allodynia was tested using von Frey filaments. Animals were placed in methacrylate cylinders on an elevated surface, with metallic mesh floor perforated in order to apply the filaments. After an acclimation period of about 30 minutes within the cylinders, both hindpaws were stimulated (the injured and the non-injured paw, serving the latter as control), starting with the lowest force filament (0.4 g) and reaching up to a 15 g filament. The animal’s response to pain was manifested by the withdrawal of the paw as a consequence of the painful stimulus caused by a filament. The pressure (force in grams) threshold eliciting the withdrawal of the paw was recorded. The analgesic effect of the test compound is seen as a (partial) restoration of the threshold toward normal.

Analysis of synergistic effect
The synergistic interaction between tramadol and celecoxib was determined by isobologram analysis as discloses by R. J. Tallarida, et al., Life Sci., 1989, 45, 947. This procedure involves the determination of the total amount in the mixture that is required to produce a specified synergistic anti-hyperalgesic effect at the 50% dose level (that is, the ED$_{50}$ or Zmix) and the corresponding total amount that would be expected under simple additivity (ED$_{50}$ add
or Zadd). Where it is established that $Z_{\text{mix}} < Z_{\text{add}}$ for a specific fixed-ratio, then that composition has a synergistic anti-hyperalgesic effect. Both $ED_{50}$ mix and $ED_{50}$ add values are random variables. $ED_{50}$ mix is determined from the dose-response curve for a specific fixed-ratio of the components; $ED_{50}$ add is calculated from the $ED_{50}$ values for the individual drugs. $Z_{\text{mix}}$ is then compared to $Z_{\text{add}}$ via a Student's $t$-test.

Results:
In this study, a dose response of co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), tramadol and celecoxib (intraperitoneal route) were obtained. Mechanical alldynia and thermal hypersensitivity were used as behavioural endpoint. All drugs induced full efficacy when mechanical alldynia was evaluated.

Results obtained on the effect in mechanical alldynia for co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), tramadol and celecoxib expressed as $ED_{50}$ are shown in Table 3 and Figure 6, whereas Figure 7 shows an isobologram of anti-alldynic interaction of celecoxib ($ED_{50} = 3.01$ mg/kg) and tramadol ($ED_{50} = 5.28$ mg/kg) on mechanical alldynia in this post-surgical pain model. Figure 8 shows results obtained on the effect of co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), tramadol and celecoxib expressed as $ED_{50}$ in the incision-induced thermal hyperalgesia in the rat hind paw. Co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) was more potent than tramadol and celecoxib.

Table 3. $ED_{50}$ (mg/kg) of each drug tested obtained after sigmoidal adjustment for mechanical alldynia and thermal hyperalgesia in a model of postoperative pain after paw incision in rats.

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Tramadol</th>
<th>Co-Crystal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural endpoint</td>
<td>Mechanical alldynia</td>
<td>3.03</td>
<td>5.41</td>
</tr>
<tr>
<td>Thermal hyperalgesia</td>
<td>2.35*</td>
<td>8.3</td>
<td>2.26</td>
</tr>
</tbody>
</table>

* $E_{\text{max}} = 47.53\%$

The isobologram of Fig. 7 is showing anti-alldynic interaction of celecoxib ($ED_{50} = 3.01$ mg/kg) and tramadol ($ED_{50} = 5.28$ mg/kg) on mechanical alldynia in the paw incision postoperative pain model in rats. The oblique line between x- and y axis is the theoretical additive line. The point in the middle of this line is the theoretical additive point calculated from separate $ED_{50}$. Grey: the experimental point (co-crystal of (rac)-tramadol·HCl - celecoxib
(1:1) ED₅₀, molecular weight ratio 1:1.27) lies far below the theoretical ED₅₀ (black), indicating a significant (P <0.05) synergistic interaction.

As shown in Fig. 8 tramadol and co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) similarly showed full efficacy when thermal hyperalgesia was used although celecoxib induced only a partial response (Emax: 45 %). Clearly co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) was more potent than tramadol (ED₅₀ Tram: 8.3 mg/kg vs ED₅₀ co-crystal of (rac)-tramadol·HCl - celecoxib (1:1): 2.26 mg/kg) in this parameter suggesting a clear synergistic effect. Isobologram analysis for this behavioural endpoint was not suitable because the ceiling effect of celecoxib (45 %).

Conclusion
Co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) administrated intraperitoneal act synergistically to inhibit both mechanical allodynia and thermal hyperalgesia in the paw incision postoperative pain model.

Example 1e: Effects on Mechanical Alldynia and Movement-Evoked Pain in an acute monoarthritic model in Rat
In this study the effects of co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), tramadol and celecoxib on mechanical allodynia and movement-evoked pain were evaluated in an acute monoarthritic rat model. Movement-evoked pain was evaluated by a computerized behavioral monitoring system (CBMS). The use of this method to assess a pain-induced gait adaptation together with the von Frey methodology to evaluate evoked-pain produces a better and more reliable picture of the animal's pain experience.

The rat carrageenan model utilizes inflammation-associated pain following injection of the knee joint (monoarthritic model). The aim of this study was to evaluate the analgesic efficacy and potency of tramadol, celecoxib and co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) in reducing pain behaviour in monoarthritic rats induced by an injection of 300µg of carrageenan into the right knee joint. The CBMS was used to assess gait related changes 5 hours after carrageenan injection and 30 min after drugs administration. Gait deficits were observed in different CBMS parameters grouped in: statics (print area, print length, print width), dynamics (stand, swing), and coordination (phase dispersion). Mechanical allodynia was measured with von Frey filaments 15 minutes after CBMS gait analysis. In this study, the effects of co-crystal of (rac)-tramadol·HCl - celecoxib (1:1), tramadol and celecoxib were evaluated due to their common prescription for moderate to severe pain associated with injury or inflammation in the clinic.
Experimental design:

Animals
Male, Wistar rats (225–250 g, Charles River Laboratories) were housed in a climate-controlled room. Food and water were available ad libitum up to test time.

Animal Dosing
Rats were all dosed intraperitoneally with co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) or each agent tramadol hydrochloride and celecoxib separately, dissolved in a suspension of 0.5% hydroxypropyl methylcellulose in distilled water. The dosing volume was 2 ml/kg. The drug response of the animal was subsequently evaluated 30 and 45 min after drug administration (for CBMS and von Frey respectively).

Knee joint monoarthritis induced by intraarticular injection of carrageenan.
Joint inflammation was induced by carrageenan (Sigma Chemical, St. Louis, MO) injected percutaneously using a 30-gauge needle through the infrapatellar ligament into the right knee joint cavity (300 μg, 40 μl) with the animal under brief isoflurane (IsoFlo®, Abbott-Esteve, Barcelona, Spain) anaesthesia (3%).

Assessment of pain-induced gait adaptation with CBMS method.
Detailed analysis of gait was performed on walking rats using the CBMS method. Briefly, light from a fluorescent tube is sent through a glass plate. Light rays are completely reflected internally. As soon as anything, e.g. a rat’s paw, is in contact with the glass surface, light is reflected downwards. It results in a sharp image of a bright paw print. The whole run is recorded via a camera placed under the glass plate.

In the present study, parameters related to single paws were analyzed:
- **Print Area (expressed in mm²)**: This parameter describes the total floor area contacted by the paw during the stance phase.
- **Max Contact Area (expressed in mm²)**: The maximal contact area describes the paw area contacted at the moment of maximal paw-floor contact, during stance.
- **Print Width (expressed in mm)**: It is a measure of the width of the print area.
- **Print Length (expressed in mm)**: It is a measure of the length of the print area.
- **Stand (expressed in s)**: It is the duration in seconds of contact of a paw with the glass plate.
- **Swing (expressed in s)**: It is the duration in seconds of no contact of a paw with the glass plate.
- **Swing Speed (expressed in m/s)**: It is the speed (Distance Unit/second) of the paw during Swing. This parameter is computed from stride length and swing duration.
- **Duty cycle (%)**: It expresses Stand as a percentage of Step Cycle.
- **Stand Index**: It is a measure for the speed at which the paw loses contact with the glass plate.
- **Max Contact at** (expressed in seconds): It is the time in seconds since the start of the run that a paw makes maximum contact with the glass plate. It can be regarded as the point at which the braking phase turns into the propulsion phase during Stand.

**Assessment of mechanical hypersensitivity (alldynia) in monoarthritic rats.**
Mechanical alldynia was tested using von Frey filaments: Animals were placed in methacrylate cylinders on an elevated surface, with metallic mesh floor perforated in order to apply the filaments. After an acclimation period of about 15 minutes within the cylinders, both hindpaws were stimulated (the injured and the non-injured paw, serving the latter as control), starting with the lowest force filament (0.4 g) and reaching a 15 g filament. The animal’s response to pain was manifested by the withdrawal of the paw as a consequence of the painful stimulus caused by a filament. The pressure (force in grams) threshold eliciting the withdrawal of the paw was recorded. The analgesic effect of the test compound is seen as a (partial) restoration of the threshold toward normal.

**Results:**
Arthritis caused by injection of carrageenan (CAR) into an ankle joint caused a change in several parameters describing the way rats walk, indicating an unwillingness to use the injected paw. CAR-induced gait changes were inhibited by celecoxib, tramadol and co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) (Fig. 9).
The results showed that co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) administration produced greater beneficial effects (relative to the individual administration of tramadol and celecoxib) in various CBMS-associated parameters including: print area, print length, maximal contact area, stand index, and phase dispersion.

Fig. 9 shows the effects of a co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) [the right column in each triplet of bars], of tramadol [the central/middle column in each triplet of bars] and of celecoxib [the left column in each triplet of bars] given intraperitoneally 4.5 h after induction by carrageenan (n = 8-10 per dose group), on motor behaviour of monoarthritic rats measured walking across the CBMS 30 min after drugs administration. As outlined above the co-crystal was given at the dose of 20 mg/kg and (rac)-tramadol·HCl or celecoxib given alone at the dose corresponding to which it is present in the co-crystal. Print Area (expressed in mm$^2$) describes the total floor area contacted by the paw during the stance phase. Max Contact Area describes the paw area contacted at the moment of maximal paw-floor contact,
during stance. Print Length is a measure of the length of the print area. Stand is the duration in seconds of contact of a paw with the glass plate. Stand Index is a measure for the speed at which the paw loses contact with the glass plate. Swing Speed is the speed (Distance Unit/second) of the paw during Swing. This parameter is computed from stride length and swing duration. Max Contact at is the time in seconds since the start of the run that a paw makes maximum contact with the glass plate. It can be regarded as the point at which the braking phase turns into the propulsion phase during Stand. Phase Dispersion Girdle is a parameter about interlimb coordination using the timed relationships between footfalls of two different paws. All data are presented as means ± SEM. * p<0.05 co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) vs Tramadol; # p<0.05 co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) vs Celecoxib.

**Conclusion**

Co-crystal of (rac)-tramadol·HCl - celecoxib (1:1) produced a superior benefit over the single drugs tested in various pain-induced gait changes in a rat model of acute monoarthritic pain.
Claims:

1. A co-crystal comprising tramadol either as a free base or as a physiologically acceptable salt and at least one coxib.

2. A co-crystal according to claim 1, wherein the coxib is chosen in such a way that if compared to either tramadol alone, or to a mixture of tramadol and the corresponding coxib, as active agent/s:
   - the solubility of the co-crystal is increased; and/or
   - the dose response of the co-crystal is increased; and/or
   - the efficacy of the co-crystal is increased; and/or
   - the dissolution of the co-crystal is increased; and/or
   - the bioavailability of the co-crystal is increased; and/or
   - the stability of the co-crystal is increased; and/or
   - the hygroscopicity of the co-crystal is decreased; and/or
   - the form diversity of the co-crystal is decreased; and/or
   - the morphology of the co-crystal is modulated.

3. The co-crystal according to any of claims 1 or 2, wherein the NSAID is selected from:
   - Celecoxib,
   - Etoricoxib,
   - Lumiracoxib,
   - Parecoxib,
   - Rofecoxib,
   - Valdecoxib, or
   - Cimicoxib.

4. The co-crystal according to any of claims 1 to 3, wherein the tramadol is (-)-tramadol or (+)-tramadol or is (rac)-tramadol or a salt thereof.

5. The co-crystal according to any of claims 1 to 4, wherein the coxib is celecoxib or salts thereof.

6. A co-crystal according to claim 5, selected from:
   - a co-crystal comprising (rac)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;
• a co-crystal comprising (+)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib;
• a co-crystal comprising (-)-tramadol either as a free base or as a physiologically acceptable salt and celecoxib; or preferably
• a co-crystal comprising (rac)-tramadol·HCl and celecoxib.

7. The co-crystal according to any of claims 1 to 6, comprising (rac)-tramadol·HCl and celecoxib.

8. The co-crystal according to claim 7, wherein the molecular ratio between the (rac)-tramadol·HCl and celecoxib is 1:1.

9. A co-crystal according to claim 8 comprising (rac)-tramadol·HCl and celecoxib in a molecular ratio of 1:1, characterized in that it shows a Powder X-Ray Diffraction pattern with peaks [2θ] at 7.1, 9.3, 10.2, 10.7, 13.6, 13.9, 14.1, 15.5, 16.1, 16.2, 16.8, 17.5, 18.0, 19.0, 19.5, 19.9, 20.5, 21.2, 21.3, 21.4, 21.8, 22.1, 22.6, 22.7, 23.6, 24.1, 24.4, 25.2, 26.1, 26.6, 26.8, 27.4, 27.9, 28.1, 29.1, 29.9, 30.1, 31.1, 31.3, 31.7, 32.5, 32.8, 34.4, 35.0, 35.8, 36.2 and 37.2[°], with the 2θ values being obtained using copper radiation (CuKα, 1.54060Å).

10. A co-crystal according to claim 8 comprising (rac)-tramadol·HCl and celecoxib in a molecular ratio of 1:1, characterized in that it shows a Fourier Transform Infra Red pattern with absorption bands at 3481.6 (m), 3133.5 (m), 2923.0 (m), 2667.7 (m), 1596.0 (m), 1472.4 (m), 1458.0 (m), 1335.1 (m), 1288.7 (m), 1271.8 (m), 1168.7 (s), 1237.3 (m), 1168.7 (s), 1122.6 (s), 1100.9 (m), 1042.2 (m), 976.8 (m), 844.6 (m), 820.1 (m), 786.5 (m) 625.9 (m) cm⁻¹.

11. A co-crystal according to claim 8 comprising (rac)-tramadol·HCl and celecoxib in a molecular ratio of 1:1, characterized in that it has an orthorhombic unit cell with the following dimensions:

a = 11.0323(7) Å
b = 18.1095(12) Å

12. A co-crystal according to claim 8 comprising (rac)-tramadol·HCl and celecoxib in a molecular ratio of 1:1, characterized in that it has a monoclinic unit cell with the following dimensions:

a = 11.0323(7) Å
12. A co-crystal according to claim 8 comprising (rac)-tramadol·HCl and celecoxib in a molecular ratio of 1:1, characterized in that the endothermic sharp peak corresponding to the melting point has an onset at 164°C.

13. Process for the production of a co-crystal according to claim 1 comprising the steps of:

(a) dissolving or suspending the coxib in a solvent; optionally heating the solution or dispersion to a temperature above ambient temperature and below the boiling point of the solution or dispersion;
(b) dissolving together with, or after, or before step (a) tramadol either as a free base or as a salt in a solvent, optionally combined with step (a) by dissolving tramadol already together with the coxib in step (a)
(c) optionally adding the solution of (b) to the solution of (a) and mixing them;
(d) optionally adding a solvent to the solution of (a), (b) or (c) and mixing them;
(e) cooling the mixed solution/dispersion of step (a), (b), (c) or (d) to ambient temperature or below;
(f) optionally evaporating part or all of the solvent; and
(g) filtering-off the resulting co-crystals.

14. Pharmaceutical composition characterized in that it comprises a therapeutically effective amount of the co-crystal according to any of claims 1 to 12 in a physiologically acceptable medium.

15. A co-crystal according to any one of claims 1 to 12 for the treatment of pain, preferably acute pain, chronic pain, neuropathic pain, nociceptive pain, mild and severe to moderate pain, hyperalgesia, pain related to central sensitization, allodynia or cancer pain, including diabetic neuropathy or diabetic peripheral neuropathy and osteoarthritis, fibromyalgia; rheumatoid arthritis, ankylosing spondylitis, frozen shoulder or sciatica.
Fig. 8)

Postoperative pain
Thermal Hyperalgesia

- Co-Crystal (ED50=2.26)
- Celecoxib (ED50=2.35). Emax=47.53%
- Tramadol (ED50=8.30)
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/135 A61K31/415 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)
A61K 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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search 30 June 2010

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Name and mailing address of the ISA/ European Patent Office, P. B. 5816 Patentlaan 2 NL-2280 HV Hilversum Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

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