



(51) International Patent Classification:

A61K 31/137 (2006.01) A61K 31/724 (2006.01)
A61K 9/20 (2006.01) A61K 9/28 (2006.01)

(21) International Application Number:

PCT/EP2013/066252

(22) International Filing Date:

2 August 2013 (02.08.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12005703.9 6 August 2012 (06.08.2012) EP
61/679,847 6 August 2012 (06.08.2012) US

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

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

Published:

— with international search report (Art. 21(3))

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING TAPENTADOL AND CYCLODEXTRIN

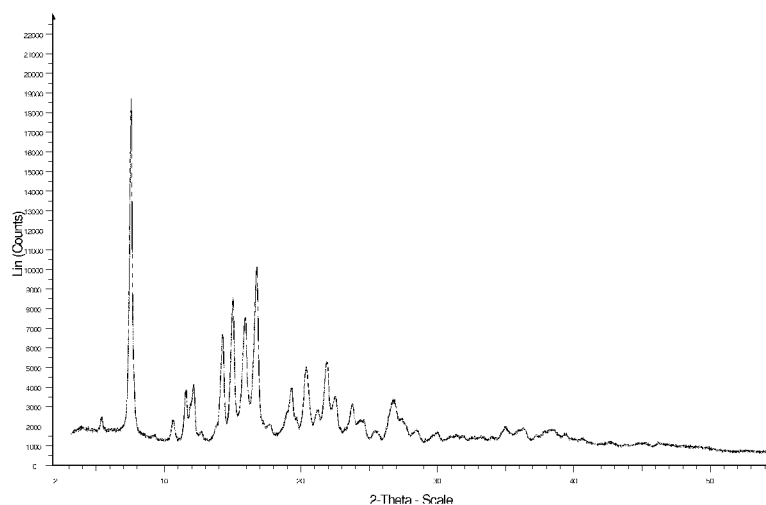


Figure A- 3 : X-Ray powder diffraction spectrum of tapentadol/ γ -cyclodextrin inclusion complex

(57) Abstract: The present invention relates to a pharmaceutical formulation comprising tapentadol and cyclodextrin. The invention further relates to a process for producing said pharmaceutical formulations. Finally, the invention relates to the use of cyclodextrin for producing a tapentadol-containing pharmaceutical formulation, wherein the pharmaceutical formulation has a dissolution of at least 0% after 15 min.

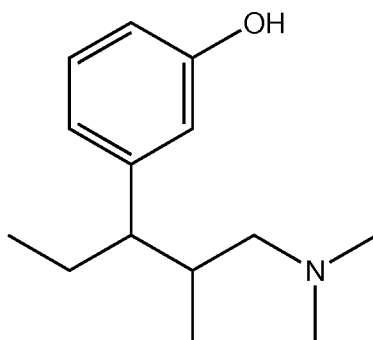
Pharmaceutical Formulation Comprising Tapentadol and Cyclodextrin

Background of the invention

The present invention relates to a pharmaceutical formulation comprising tapentadol and cyclodextrin. The invention further relates to a process for producing said pharmaceutical formulations. Finally, the invention relates to the use of cyclodextrin for producing a tapentadol-containing pharmaceutical formulation, wherein the pharmaceutical formulation has a dissolution of at least 50% after 15 min.

Tapentadol is an analgesic whose effect is based on two molecular mechanisms. First of all, like opioids, tapentadol activates μ -receptors and thus presynaptically and postsynaptically attenuates the transmission of pain stimuli in the spinal cord and brain. Secondly, tapentadol acts as a noradrenalin re-uptake inhibitor and thus increases the concentration of that nerve messenger in the synaptic gap.

In the context of this invention, the term "tapentadol" is understood to mean 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol in accordance with the following chemical formula (1).

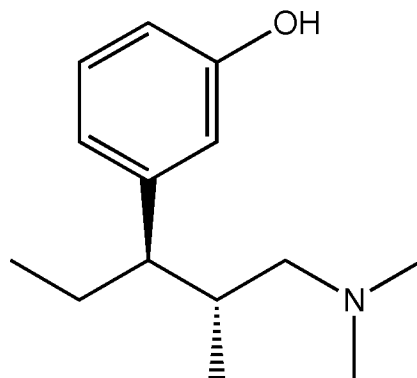


formula (1)

3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol has two centres of asymmetry, so that the compound can be present in the form of four different stereoisomers. In the context of this invention, 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol may be present as a mixture of all four diastereomers in any mixing ratio, but also as a mixture of two or three of the four stereoisomers or in stereoisomerically pure form. Preferred stereoisomers in this context are (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol and (-)-(1R,2R)-3-(3-

dimethylamino-1-ethyl-2-methyl-propyl) phenol, which can preferably be used as a 1:1 mixture (racemate) or particularly preferably in isomerically pure form. In particular, (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol (hereinafter also referred to as “(1R,2R)-tapentadol”) according to formula (2) is used.

5



formula (2)

10 Synthesis pathways for crystalline tapentadol and its use as an analgesic have been described in EP 0 693 475 A1.

Due to the good water solubility of the respective tapentadol salts the active agent is generally used for the preparation of pharmaceutical formulations in form of an acceptable pharmaceutical salt, usually as tapentadol hydrochloride. There are at least two polymorphic forms of tapentadol hydrochloride, namely crystalline form (A) and form (B), which can be distinguished by X-ray diffraction. However, when developing tapentadol formulations the inventors of the present application were confronted with the fact that said individual polymorphs are reported not to be stable. The above-mentioned forms (A) and (B) of tapentadol hydrochloride may be partially or completely interconverted by the influence of environmental conditions, such as temperature. The frequently used tapentadol hydrochloride form (A), for example, can be changed into form (B) under the influence of heat, see WO 2006/00441 A2. This process is reversible when the temperature is lowered. However, this limited solid-state stability of an active ingredient may result in unpredictable biopharmaceutical characteristics, such as uneven rise in the concentration of the active agent.

US 2010/0272815 is related to an allegedly stable form of amorphous tapentadol hydrochloride and an amorphous co-precipitate comprising tapentadol hydrochloride and a pharmaceutically acceptable excipient, wherein the content of crystalline tapentadol is preferably less than 5%. Further, processes for the

preparation of the amorphous tapentadol hydrochloride and the above mentioned amorphous co-precipitates and their use in pharmaceutical formulations are described.

- 5 WO 2009/071310 describes the polymorphous forms A, B, C of tapentadol as a free base and pharmaceutical formulations containing them. However, these polymorphs show poor water solubility compared to the above-mentioned tapentadol hydrochloride. Further, also these polymorphs of the tapentadol as a free base tend to interconvert. Moreover, they exhibit different solubility profiles.
- 10 Different solubility profiles, however, may lead to an undesirable, uneven rise in the concentration of the active agent.

Hence, it was an object of the present invention to overcome the drawbacks of the above-mentioned formulation.

- 15 In particular, it was an object of the present invention to provide tapentadol in a form in which it can be processed into a dosage form which (even after storage) enables as even a rise as possible in the concentration in the patient. The aim was largely to avoid both inter-individual and also intra-individual deviations.

- 20 Further, the intention is to provide the active agent in a form possessing good processability, such as flowability, and thus making it possible to ensure good compression into tablets, even with solvent-free manufacturing processes.

- 25 It is also the intention to provide the active agent in a form which does not have a tendency to agglomerate.

Further, in one embodiment the use of tapentadol salts should be avoided. In particular, the use of tapentadol hydrochloride should be avoided.

- 30 Furthermore, it was an object of the invention to provide tapentadol in a form having superior storage properties. Preferably, storage stability for 12 months at 40°C and 75% humidity should be achieved.

- 35 Finally, the intention is also to provide dosage forms of tapentadol which ensure good solubility and bioavailability with good storage stability at the same time.

In particular, tapentadol free base should be provided in a form having superior solubility and superior permeability. Preferably, tapentadol should be provided in a

form which is regarded as a BCS class I agent (high permeability, high solubility). In addition, tapentadol should be provided in a form which allows oral application. The increase in solubility and permeability should be achieved without a micronization step, due to the undesired poor flowability of most micronized products.

All the above-mentioned objectives are supposed to be solved both for a formulation designed for immediate release (or “IR” for short) and for modified release (or “MR” for short).

Summary of the invention

According to the present invention, the above objectives can be achieved by a composition comprising tapentadol, preferably in form of the free base, and cyclodextrin. In the composition of the present invention tapentadol preferably is present in form of a complex and can be advantageously processed into pharmaceutical formulations like tablets.

Thus, the subject of the invention is a composition comprising (a) tapentadol, preferably tapentadol as a free base, and (b) cyclodextrin.

A further subject of the present invention is a pharmaceutical formulation, preferably in the form of an oral dosage form, comprising the composition of the invention and optionally one or more pharmaceutical excipient(s).

A further subject of the present invention is a process for producing a tapentadol/cyclodextrin composition comprising the steps of

- i) dissolving and/or dispersing (a) tapentadol and (b) cyclodextrin in a solvent,
- ii) optionally homogenizing the solution or dispersion from step i), and
- iii) removing the solvent and optionally isolating the resulting composition.

Further the subject of the present invention relates to a process for preparing a pharmaceutical formulation comprising the steps:

- I) providing the composition of the invention
- II) optionally adding further excipient(s) (c) to the composition of step I),
- III) processing the mixture of step I) or II) to a solid oral dosage form
- IV) optionally film-coating the oral dosage form.

The above-illustrated subjects of the present invention are alternative solutions to the above-outlined problems.

Detailed Description of the Invention

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The term "tapentadol" as used in the present application can refer to tapentadol according to the above formulae, preferably according to formula (2). Alternatively, it can refer to pharmaceutically acceptable salts, solvates, hydrates, polymorphs and mixtures thereof. Preferably, tapentadol is used in the form of the free base, i.e. as a compound as shown in formula (1) or (2). In a preferred embodiment of the present invention tapentadol is not used in form of the hydrochloride. Within the present application, ratios or amounts of tapentadol generally refer to the ratio or amount of tapentadol in form of the free base.

10

15 In a particularly preferred embodiment the composition of the present invention as well as the pharmaceutical formulation of the present invention comprise tapentadol as the sole pharmaceutical active agent. In an alternative embodiment the composition of the present invention as well as the pharmaceutical formulation of the present invention can comprise tapentadol in combination with further
20 pharmaceutical active agent(s).

20

In line with the present application the term "cyclodextrin" may refer to non-reducing cyclic saccharides and mixtures thereof. Preferably, said cyclic saccharides comprise six, seven, eight or nine glucose units, linked by alpha-1,4
25 interglycosidic bonds.

25

Cyclodextrin can be a naturally occurring cyclodextrin or a chemically modified cyclodextrin. The cyclodextrins of the present invention can be (partially) substituted. Substitution can be achieved with acetyl groups, alkoxy groups such as
30 carboxymethyl, heteroaromatic or aromatic groups such as benzyl, heteroalkyl or alkyl groups, preferably C₁-C₈ alkyl groups such as methyl, ethyl, propyl, butyl and pentyl, or with hydroxyalkyl groups such as hydroxyethyl and hydroxypropyl. Preferably, the cyclodextrins can be (partially) substituted with hydroxypropyl groups.

30

35

The average degree of substitution is usually 0.1 to 3, preferably 0.3 to 2, more preferably 0.4 to 1.5 and most preferably 0.5 to 1 per glucose unit. In case (2-hydroxy)propyl- β -cyclodextrin is used, the degree of substitution is 0.1 to 2,

preferably 0.3 to 1.5 and most preferably 0.5 to 1 of hydroxypropyl groups per glucose unit.

Examples of cyclodextrins are α -cyclodextrin, β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin (HPBCD), randomly methylated β -cyclodextrin, sulfobutylether- β -cyclodextrin (SBEBCD), γ -cyclodextrin and 2-hydroxypropyl- γ -cyclodextrin (HPGCD). Preferred are α -cyclodextrin, β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin (HPBCD) and γ -cyclodextrin.

Furthermore, it is particularly preferred that in all embodiments of the present invention cyclodextrins can be used in the form of cyclodextrin hydrate, for example α -cyclodextrin and γ -cyclodextrin. In a preferred embodiment the water content of the cyclodextrin used for making the inclusion complex can be less than 15 wt.-%, preferably 1 to 12 wt.-%, most preferably 1 to 8 wt.-%, based on the total weight of the cyclodextrin.

In a preferred embodiment of the composition tapentadol (a) and cyclodextrin (b) are present in the form of a complex, preferably in form of an inclusion complex. The complex, preferably the inclusion complex, can preferably lead to a novel solid of tapentadol, preferably to a form of molecular dispersity.

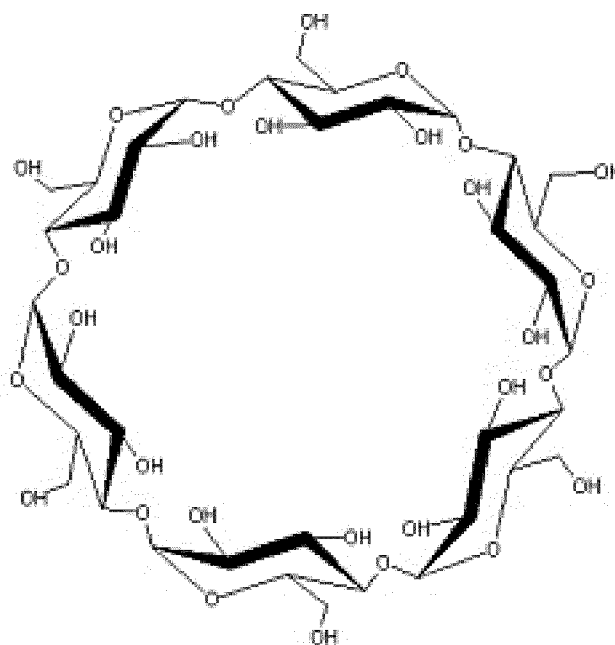
The novel solid form of tapentadol can be regarded as tapentadol in form of a solid solution of tapentadol. This novel solid form of tapentadol is preferably a stabilized and/or hydrophilized form of the active agent. Further the form can be described as a glassy/non-crystalline solid form.

In a preferred embodiment of the invention, the present invention can refer to a tapentadol-cyclodextrin inclusion complex, preferably to a "genuine" tapentadol-cyclodextrin inclusion complex. The term "genuine" indicates that the entire and complete amount of tapentadol can be entrapped intercalated in the molecular cavities of the cyclodextrin, i.e. tapentadol is only present in intercalated form. No adsorbed, un-entrapped crystalline or amorphous tapentadol occurs. The formation of the preferred "genuine" inclusion complex generally can lead to the above-mentioned glassy/non-crystalline solid form of tapentadol.

Since, as mentioned above, tapentadol can be included, preferably completely included in the cavity, the cyclodextrin "shell" can prevent the tapentadol from negative environmental influences, as for example ultraviolet radiation and oxygen. Therefore, the stability of the tapentadol in the complex can be increased.

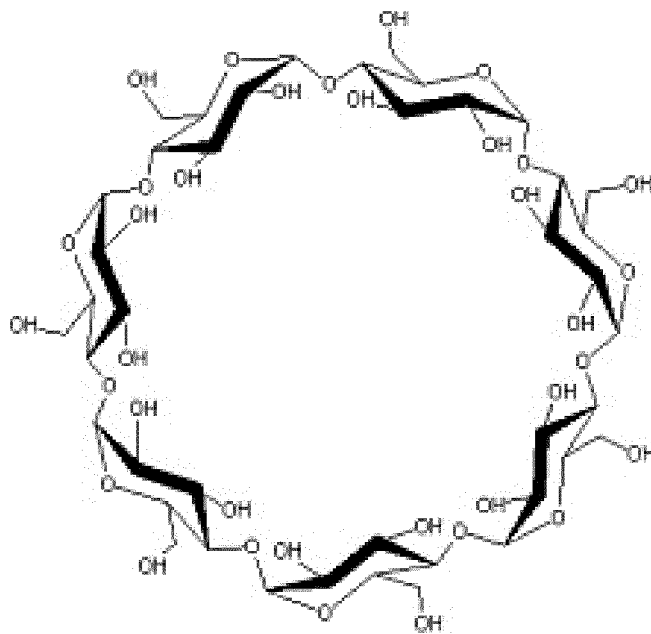
Preferably, all preferred inclusion complexes of the present invention can be non-covalent inclusion complexes. Furthermore, all preferred inclusion complexes of the present invention can be supramolecular inclusion complexes. In particular, all preferred inclusion complexes of the present invention can be non-covalent and
5 supramolecular inclusion complexes. The term “supramolecular” is understood as describing self-organizing molecular interactions that result in the formation of new structures that stay together without establishing a covalent linkage.

In a preferred embodiment of the present invention a tapentadol complex, preferably a tapentadol inclusion complex, can be achieved by the use of α -cyclodextrin, preferably α -cyclodextrin hydrate. α -cyclodextrin is a ring-shaped molecule, made up of six glucose units and linked by alpha-1,4 bonds. α -cyclodextrin can be characterized by the following chemical formula (3):



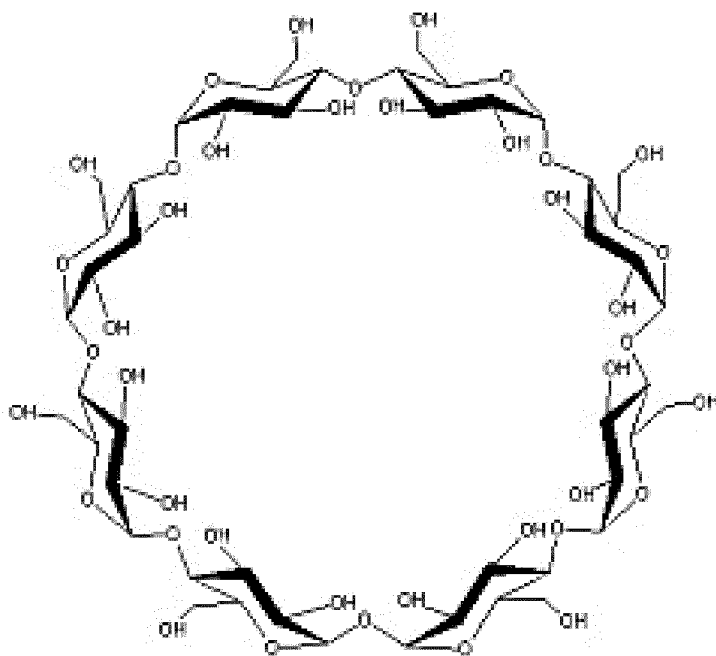
formula (3)

In preferred embodiment of the present invention a tapentadol complex, preferably a tapentadol inclusion complex, can be achieved by the use of β -cyclodextrin, preferably β -cyclodextrin hydrate. β -cyclodextrin is a ring-shaped molecule made up of seven glucose units linked by alpha-1,4 bonds. β -cyclodextrin can be characterized by the following chemical formula (4):



formula (4)

- In an alternative preferred embodiment of the present invention a tapentadol composition, preferably a tapentadol inclusion complex, can be achieved by the use of 2-hydroxypropyl- β -cyclodextrin (HPBCD). 2-hydroxypropyl- β -cyclodextrin (HPBCD) is also a ring-shaped molecule made up of seven glucose units linked by α -1,4 bonds, wherein 4 to 5 of the hydroxy groups are 2-hydroxypropylated.
- Alternatively preferred, a tapentadol-cyclodextrin inclusion complex of the present invention can be achieved when γ -cyclodextrin is used. γ -cyclodextrin is a ring-shaped molecule, made up of eight glucose units, linked by α -1,4 bonds. γ -cyclodextrin can be characterized by the following chemical formula (5):



formula (5)

The term “ γ -cyclodextrin” preferably refers to a “non-substituted form” (as shown in the above formula). This means, the γ -cyclodextrin preferably is not chemically modified, i.e. neither alkylated nor hydroxyl-alkylated. Moreover, preferably γ -cyclodextrin having a bulk density of from 400 to 700 mg/cm³ is used. The bulk density can be determined according to Ph.Eur. 6.0, in particular, Chapter 2.9.15.

Furthermore, as mentioned above, the γ -cyclodextrin can preferably be used in the form of a crystalline hydrate. Furthermore, it is preferred that γ -cyclodextrin can be used in the form of a hydrate, wherein each molecule of γ -cyclodextrin comprises between 12 and 14 molecules of water. Generally, γ -cyclodextrins can exist in two main classes of crystal structures, namely the cage and tubular (or columnar) structure. In the cage structure (often called also a “HERRING BONE arrangement”), the cyclodextrin cavities are not aligned. Contrary, in the tubular structure, γ -cyclodextrin monomers stick to each other on their top, forming a cylindrical multi-molecular channel, where, for example, slim but long molecules (for example linear polymers) could fit in and form a stable complex. In the present invention it is preferred that γ -cyclodextrin having a cage structure can be used. In addition, crystalline γ -cyclodextrin having a monoclinic space group can preferably be used.

In a preferred embodiment of the invention, the cyclodextrin has a water-solubility at 25°C of from 15 to 1000 mg/ml, preferably 50 to 800 mg/ml and more preferably 100 to 650 mg/ml. The water-solubility can be determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC),
5 Annex V, chapter A6.

The composition of the present invention can preferably have a molecular ratio of tapentadol (a) to cyclodextrin (b) from 5:1 to 1:10, preferably from 3:1 to 1:8, more preferably from 2:1 to 1:5, most preferably from 1:1 to 1:3.

10 Generally, the composition of the present invention comprising a) tapentadol and b) cyclodextrin can be achieved if the molecular ratio of tapentadol (a) to cyclodextrin (b) is as mentioned above. In a further preferred embodiment tapentadol (a) and the cyclodextrin (b) may form a complex, preferably an
15 inclusion complex, especially a “genuine” inclusion complex, in which the molar ratio of tapentadol to cyclodextrin is preferably from 0.5:1 to 2:1, preferably from 0.7:1 to 1.5:1, more preferably from 0.8:1 to 1.2:1, especially about 1:1.

20 The average particle size of cyclodextrin-tapentadol complexes, preferably inclusion complexes, such of the γ -cyclodextrin tapentadol inclusion complexes, can be between 2 and 100 μm , preferably between 5 and 25 μm and particularly between 6 and 15 μm .

25 The term “average particle size” refers to the D_{50} value of the particle size distribution, which is determined by the light scattering method, using a Mastersizer 2000 apparatus made by Malvern Instruments (wet measurement, 2000 rpm, ultrasonic waves for 60 sec., data interpretation via Fraunhofer method).

30 The volume mean particle size (D_{50}), which is also denoted D_{50} value of the integral volume distribution, is defined in the context of this invention as the particle diameter at which 50 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D_{50} value. Likewise, 50 percent by volume of the particles have a larger diameter than the D_{50} value. Analogous, the D_{90} value of the integral volume distribution is defined as the
35 particle diameter, at which 90 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D_{90} value. Correspondingly, the D_{10} value of the integral volume distribution is defined as the particle diameter at which 10 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D_{10} value.

Furthermore, the cyclodextrin-tapentadol complexes, preferably inclusion complexes, of the present invention preferably can be provided in a solid form having a bulk density of from 100 to 900 mg/cm³, preferably from 120 to 800 mg/cm³, more preferably from 140 to 700 mg/cm³, especially from 150 to 600 mg/cm³.

The tapentadol-cyclodextrin complexes, preferably inclusion complexes, can be regarded as a glassy-amorphous solid phase of tapentadol. The glassy-amorphous solid phase of tapentadol, re-wetted in an aqueous system, preferably can show some liquid crystalline properties that remind of the lyotropic liquid crystalline material.

When viewed under a polarized light, different liquid crystal phases can appear, having a distinct Schlieren texture. The contrasting areas in the texture each correspond to a domain, where the liquid crystalline molecules are oriented in a different direction. Within a domain, however, the molecules can be well ordered. The polarized light microscopic photos taken from the tapentadol/ γ -cyclodextrin complex of this invention can clearly indicate the specific, liquid crystalline-like mesophase texture.

The composition, preferably the complex, more preferably the inclusion complex comprising tapentadol and cyclodextrin can preferably be present in a crystalline form.

In an alternative preferred embodiment the composition, preferably the complex, more preferably the inclusion complex comprising tapentadol and cyclodextrin can preferably be present in a non-crystalline form.

The present invention further relates to a process for producing a composition comprising tapentadol and cyclodextrin, preferably as complex, more preferably as inclusion complex. Hence, a further subject of the present invention can be a process for producing a composition comprising tapentadol and cyclodextrin, comprising the steps of

- i) dissolving and/or dispersing tapentadol and cyclodextrin in a solvent;
- ii) optionally homogenizing the solution or dispersion from step (a); and
- iii) removing the solvent and optionally isolating the composition

Generally, the comments made above for tapentadol and cyclodextrin can also apply to the process of the present invention. Thus, for example, β -cyclodextrin or (2-hydroxy)propyl- β -cyclodextrin, particularly having the above-illustrated water content, can be used in the process of the present invention.

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In step i) of the process of the invention cyclodextrin and tapentadol can be dissolved or dispersed, preferably completely dissolved, in a suitable solvent. In a preferred embodiment one or more pharmaceutical excipients (c) may also be dissolved in the above-mentioned solvent. The solvent may be water or an organic solvent or a mixture thereof. Generally, suitable organic solvents might be selected from C₃-C₆ ketone, a C₅-C₉ aliphatic or aromatic hydrocarbon, optionally substituted for example with halogen, a C₃-C₆ ester, a C₂-C₆ alcohol, C₂-C₆ ether, DMAc, DMSO, NMP and mixtures thereof.

10

15 In a preferred embodiment the organic solvent is an alcohol, preferably a C₂-C₆ alcohol, still more preferably ethanol and isopropyl alcohol. Ethanol is particularly preferred.

20 In a preferred embodiment the solvent can be a mixture of alcohol and water, wherein the mixing ratio alcohol to water is for example from 1:5 to 5:1.

Generally, the organic solvent can comprise mixtures of two or more of the above - mentioned solvents.

25 The term "dissolving or dispersing" means that a substance, such as cyclodextrin and/or tapentadol, is brought into contact with the solvent, preferably with the water, wherein the solvent wets the surface of the substance or the substance can be dispersed (i.e. suspended and optionally partially dissolved) in the solvent or, in a preferred embodiment, the substance, preferably cyclodextrin, can be completely dissolved in the solvent.

30

The weight ratio of cyclodextrin to solvent can range from 1:10 to 10:1, preferably from 1:1 to 1:5.

35 In a preferred embodiment cyclodextrin can be dissolved or dispersed in a solvent, preferably under stirring during the dissolving or dispersing step, preferably at a stirring speed from 300 to 450 rpm (rotations per minute). Further, tapentadol can be added preferably in crystalline form. More preferably, tapentadol can be added as tapentadol (partially or completely) dissolved in a solvent or co-solvent. The

solvent or co-solvent can be the same or different as the one used for dissolving or dispersing cyclodextrin.

In optional step ii) the solution or dispersion from step i) can preferably be homogenized. During the homogenization the tapentadol composition, preferably the complex, more preferably the inclusion complex, may be formed. Homogenizing can be achieved by subjecting the solution or dispersion from step i) for example to a mechanical treatment.

Generally, any mechanical treatment can be suitable to enable the inclusion of the tapentadol into the cavity of the cyclodextrin. Preferably, the mechanical treatment step can comprise ultrasonic treatment, optionally combined with stirring. Alternatively, but also preferred, mechanical treatment can be carried out by grinding, preferably by co-grinding wetted and/or dispersed cyclodextrin with tapentadol.

Generally, ultrasonic treatment can be carried out by immersing the mixture resulting from step i) into an ultrasonic device, for example, an ultrasonic bath. Examples of ultrasonic treatment are hydrodynamic cavitation, sono-fragmentation and/or sono-cavitation or co-grinding. For example, ultrasonic treatment can be carried out with Tesla ultrasonic equipment.

Ultrasonic treatment can preferably be performed by using ultrasonic waves having a frequency of 5 to 100 kHz, more preferably of 10 to 80 kHz. Furthermore, ultrasonic treatment is preferably performed by using ultrasonic waves having an intensity of 50 to 5000 W, more preferably 500 to 1000 W. As an example, 1000 W and 20 kHz or 500 W and 58 kHz can be used.

This means that instead of the relatively long 6-8 hours stirring time for reaching complete inclusion, which is used traditionally in the art for complexation, the stirring time can significantly be reduced by the above-mentioned sono-fragmentation or sono-cavitation process. By this high-energy ultrasonic treatment, the inclusion complexation technology can become more efficient and economic.

In addition to the ultrasonic treatment (for example hydrodynamic cavitation, sono-fragmentation or sono-cavitation), the reaction mixture may be agitated (for example using traditional propeller stirrer), preferably with a rotation speed of 300-450 rpm (rotations per minute).

As mentioned above, the mechanical treatment step can also be carried out by grinding, preferably by co-grinding, dispersed cyclodextrin with tapentadol. Generally, grinding can be carried out in known milling devices, for example a ball mill or a pin mill.

5

Usually, the mechanical treatment can be carried out for 1 to 30 minutes, preferably for 5 to 20 minutes. Furthermore, mechanical treatment can be carried out at a temperature of 5 to 50°C, preferably at room temperature (about 20°C).

- 10 Once solid phase transformation is completed, the solvent of the reaction mixture can be removed in step iii).

Generally, the methods known in the art for removing solvents are suitable. Examples of said method are filtering off the composition, evaporating the solvent, preferably under vacuum, lyophilizing, freeze-drying and spray-drying. When necessary an optional isolating step may be additionally applied.

15

- In a preferred embodiment of step iii) the residual solvent can be removed under elevated temperature and/or under reduced pressure. In a preferred embodiment the solvent is removed at a temperature of between 30 and 90°C, preferably between 35 and 75°C, more preferably between 40 and 60°C. The solvent can preferably be removed at a pressure of from 0.01 to 900 mbar, preferably from 1 to 200 mbar, more preferably from 5 to 100 mbar, still more preferably from 10 to 50 mbar, in particular from 30 to 40 mbar. At laboratory scale the duration of step iii) may range from 0.5 to 2.0 hours, preferably about 90 minutes. The removal of the solvent can be, for example, carried out in a vacuum rotary evaporator, for example a Büchi® Rotavapor.

20

25

- After removing the solvent, the compositions of the present invention, preferably as tapentadol-cyclodextrin complexes can be rewetted, dispersed or dissolved. The fastest dissolving form of the compositions of the present invention usually can be achieved if in step c) the solvent is removed by freeze-drying (lyophilisation) the inclusion complex.

30

- Steps i) to ii) can be carried out subsequently or simultaneously. In a preferred embodiment steps i) and ii) can be carried out subsequently.

35

Generally, one or more excipient(s) (c) may be added at any step of the above process.

Generally, the process of the present invention is suitable for preparing the inclusion complexes of the present invention, preferably achieving a yield of from 80 to 99%, more preferably from 90 to 98%.

- 5 In a preferred embodiment of the process of the invention the composition comprising tapentadol and cyclodextrin can be formed in the absence of excipients and/or co-solvents.

10 A further preferred embodiment of the present invention can be compositions, preferably complexes, more preferably inclusion complexes, obtainable by the above-mentioned process.

The composition of the present invention can be applied in the form of a pharmaceutical formulation.

15 Hence, a further subject of the present invention can be a pharmaceutical formulation, preferably in form of a solid oral dosage form, comprising a tapentadol composition according to the present invention and optionally one or more pharmaceutical excipient(s).

20 In another preferred embodiment of the present invention the pharmaceutical formulation can further comprise one or more excipients(s) (c), selected from surfactants (c1), wicking agents (c2), fillers (c3), binders (c4), disintegrants (c5), lubricants (c6), glidants (c7) and plasticizers (c8).

25 Surfactants (c1) can be regarded as substances lowering the interfacial tension between two phases, thus enabling or supporting the formation of dispersions or working as a solubilizer. Common surfactants are alkylsulfates (for example sodium lauryl sulfate), alkyltrimethylammonium salts, alcohol ethoxylates and the like. Surfactants can be used in an amount of 0.05 to 2% by weight, preferably of 0.1 to 1.5% by weight, based on the total weight of the pharmaceutical formulation.

35 Wicking agents (c2) can be regarded as substances with the ability to draw a biological fluid (preferably water) into a solid, preferably by physisorption. Physisorption is defined as a form of adsorption in which the solvent molecules can loosely adhere to the surfaces of the wicking agent, preferably via van der Waals interaction between the surface of the wicking agent and the adsorbed fluid molecule (preferably water). Usually, a wicking agent can do this with or without

swelling. Preferably, the wicking agent is a swelling wicking agent. Usually, a non-swelling wicking agent that attracts water will ultimately have a volume that is essentially composed of the volume of the wicking agent and the volume of water attracted to it. Usually, a swelling wicking agent will have a volume that is essentially composed of the volume of the wicking agent, the volume of water attracted to it and an additional volume created by steric and molecular forces. For example, microcrystalline cellulose can be used as wicking agent. Wicking agents (c2) can be used in an amount of 0 to 40% by weight, preferably 1 to 15 % by weight, based on the total weight of the pharmaceutical formulation.

Fillers (c3) or diluents can be used to increase the bulk volume and weight of a low-dose drug to a limit at which a pharmaceutical dosage form can be formed. Fillers should fulfil several requirements, such as being chemically inert, non-hygroscopic, biocompatible, easily processable and possessing good biopharmaceutical properties. Examples of fillers are lactose, sucrose, glucose, mannitol, calcium carbonate, cellulose and others. Fillers (c3) can be used in an amount of 0 to 60% by weight, preferably 1 to 20 % by weight, based on the total weight of the pharmaceutical formulation.

Binders (c4) may be added to the pharmaceutical formulation in order to ensure that oral dosage forms, preferably tablets, can be formed with the required mechanical strength. The binder can, for example, be starch, polyvinyl pyrrolidone or cellulose derivatives. The binding agent can be present in an amount of 0 to 40% by weight, based on the total weight of the pharmaceutical formulation.

Disintegrants (c5) are compounds, which enhance the ability of the dosage form, preferably the ability of the tablet when in contact with a liquid, preferably water, to break into smaller fragments. Preferred disintegrants are sodium carboxymethyl starch, cross-linked polyvinyl pyrrolidone (crospovidone), sodium carboxymethyl glycolate (for example Explotab[®]), swelling polysaccharide, for example soy polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, protein, for example formaldehyde-casein, sodium bicarbonate or mixtures thereof. Disintegrants can be used in an amount of 0 to 20% by weight, preferably of 1 to 10% by weight, based on the total weight of the pharmaceutical formulation.

The function of lubricants (c6) is reported to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. The lubricant is preferably a stearate or fatty acid, more preferably an earth alkali metal stearate, such as magnesium stearate. The lubricant is suitably present in an

amount of 0 to 2% by weight, preferably of about 0.1 to 1.0% by weight, based on the total weight of the pharmaceutical formulation. Lubricants can generally increase the powder flowability.

- 5 Glidants (c7) can also be used to improve the flowability. Traditionally, talc was used as glidant, but is nowadays nearly fully replaced by colloidal silica (for example Aerosil®). Preferably, the glidant agent is present in an amount of up to 3% by weight, based on the total weight of the pharmaceutical formulation. Preferably, the silica has a specific surface area of 50 to 400 m²/g, measured by
10 gas adsorption according to Ph. Eur. 6.0, Chapter 2.9.26, multipoint method, volumetric determination.

- Plasticizers (c8) usually are reported to be compounds capable of lowering the glass transition temperature (T_g) of a non-erodible material, preferably of lowering
15 T_g from 1 to 50°C. Plasticizers (c8) usually are low molecular weight compounds (having a molecular weight of 50 to 500 g/mol) and can comprise at least one hydrophilic group. Examples of suitable plasticizers are dibutyl sebacetate (DBS), Myvacet® (acetylated monoglycerides), triacetin (GTA), citric acid esters, like acetyltriethyl citrate (ATEC) or triethyl citrate (TEC), propylene glycol, dibutyl
20 phthalate, diethyl phthalate, or mixtures thereof.

- It lies in the nature of pharmaceutical recipients that they sometimes can perform more than one function in a pharmaceutical formulation. In this regard it is generally noted that due to the nature of pharmaceutical recipients it cannot be
25 excluded that a certain compound meets the requirements of more than one of the components (b) and (c1) to (c8). Therefore, cyclodextrin (b) may function as a component for forming the composition according to the invention as well as a pharmaceutical excipient (c), i.e. the fact that cyclodextrin is used as component for forming the composition according to the invention does not mean that it
30 cannot also be acting as a filler (c3).

- However, in order to enable an unambiguous distinction, it is preferred in the present application that one and the same pharmaceutical compound can only function as one of the compounds (b) or (c1) to (c8). For example, or if
35 microcrystalline cellulose functions as a wicking agent (c2), it cannot additionally function as a disintegrant (c5), even though microcrystalline cellulose also exhibits a certain disintegrating effect.

The pharmaceutical formulation of the present invention can preferably comprise the following amounts of components:

- 10 to 300 mg tapentadol, preferably 25 to 250 mg tapentadol, particularly 50 to 150 mg tapentadol,
- 10 to 1400 mg cyclodextrin, preferably 50 to 900 mg cyclodextrin, particularly 200 to 700 mg cyclodextrin,
- 0 to 250 mg binder, preferably 15 to 200 mg binder, particularly 25 to 150 mg binder,
- 0 to 25 mg glidant, preferably 1 to 15 mg glidant, particularly 2 to 7 mg glidant,
- 0 to 20 mg surfactant, preferably 2 to 15 mg surfactant, particularly 4 to 10 mg surfactant,
- 0 to 15 mg lubricant, preferably 1 to 10 mg lubricant, particularly 2 to 8 mg lubricant, and
- 0 to 125 mg disintegrant, preferably 5 to 100 mg disintegrant, particularly 10 to 75 mg disintegrant.

In a preferred embodiment the pharmaceutical formulation of the present invention can preferably comprise:

- 1 to 40 wt.% tapentadol, preferably 3 to 20 wt.% tapentadol, particularly 5 to 15 wt.% tapentadol,
- 1 to 80 wt.% cyclodextrin, preferably 10 to 65 wt.% cyclodextrin, particularly 20 to 55 wt.% cyclodextrin,
- 0 to 25 wt.% binder, preferably 2 to 20 wt.% binder, particularly 4 to 15 wt.% binder
- 0 to 5 wt.% glidant, preferably 0.1 to 1.5 wt.% glidant, particularly 0.3 to 1.0 wt.% glidant,
- 0 to 2 wt.% surfactant, preferably 0.2 to 1.6 wt.% surfactant, particularly 0.4 to 1.4 wt.% surfactant,
- 0 to 2 wt.% lubricant, preferably 0.1 to 1.3 wt.% lubricant, particularly 0.2 to 0.8 wt.% lubricant,
- 0 to 20 wt.% disintegrant, preferably 1 to 15 wt.% disintegrant, particularly 2 to 10 wt.% disintegrant,
- based on the total weight of the pharmaceutical formulation.

In a still further embodiment of the present invention the pharmaceutical formulation can be a solid oral dosage form, preferably a capsule or a tablet, more

preferably a tablet for peroral use. Alternatively, the solid oral dosage form can be filled as powder or granulate into devices like sachets or stick-packs.

Further, the pharmaceutical formulation, preferably the tablet, of the invention preferably has a content uniformity, i.e. a content of active agent(s), which lies within the concentration of 90 to 110%, preferably 95 to 105%, especially preferred from 98 to 102% of the average content of the active agents(s). The “content uniformity” is determined with a test in accordance with Ph. Eur., 6.0, Chapter 2.9.6. According to that test, the content of the active agents of each individual tablet out of 20 tablets must lie between of 90 to 110%, preferably 95 to 105%, especially 98 to 102% of the average content of the active agents(s). Therefore, the content of the active drugs in each tablet of the invention differs from the average content of the active agent by at most 10%, preferably at most 5% and especially at most 2%.

In addition, the resulting tablet preferably has a friability of less than 5%, particularly preferably less than 2%, especially less than 1%. The friability is determined in accordance with Ph. Eur., 6.0, Chapter 2.9.7. The friability of tablets generally refers to tablets without coating.

The pharmaceutical formulation of the invention may be a peroral tablet, which can be swallowed unchewed. The tablet can preferably be film coated.

Generally, film coatings that do not affect the release of the active agent(s) and film coatings affecting the release of the active agent(s) can be employed with tablets according to invention. The film coatings that do not affect the release of the active agent(s) are preferred.

Preferred examples of film coatings which do not affect the release of the active ingredient can be those including poly(meth)acrylate, methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP) and mixtures thereof. These polymers can have a weight-average molecular weight of 10,000 to 150,000 g/mol.

In an alternative preferred embodiment, the film coating can affect the release of the active agent. Examples for film coatings affecting the release of the active agent are gastric juice-resistant film coatings and retard coatings.

Further, the coating can be free from active ingredient. However, it is also possible that the coating can contain an active ingredient (tapentadol). In such a case, this amount of active ingredient would function as an initial dose. In such a case, the coating preferably can comprise 1 to 20 wt.%, preferably 2 to 15 wt.%, more preferably 3 to 10 wt.% of tapentadol, based on the total amount of tapentadol contained in the tablet.

In the preferred case that the film coating does not contain an active agent (a) or (b), said coating can have a thickness of 2 μm to 100 μm , preferably from 20 to 60 μm . In case of a coating containing an active agent (a) or (b), the thickness of the coating is usually 10 μm to 200 μm , preferably from 50 to 125 μm .

The tablets of the invention preferably can have a hardness of 25 to 250 N, particularly preferably of 30 to 180 N, more preferably 40 to 150 N. The hardness is determined in accordance with Ph.Eur., 6.0, Chapter 2.9.8.

In a possible embodiment the pharmaceutical formulation of the invention is for modified release. In that case the release profile of the pharmaceutical formulation, preferably of the tablet, according to USP method (USP paddle apparatus, 900 ml test medium, in phosphate buffer at pH 6.8 and 37°C, 100 rpm) after 2 hours indicates a content release of 0 to 90 %, preferably of 10 to 80 %, further preferably 15 to 75%, more preferably 20 to 50% and particularly of 25 to 40 %.

In a preferred embodiment of the invention the pharmaceutical formulation is for immediate release. In that case the release profile of the pharmaceutical formulation, preferably of the tablet, according to USP method (USP paddle apparatus, 900 ml test medium, in phosphate buffer at pH 6.8 and 37°C, 100 rpm) after 15 minutes indicates, a content release of at least 50%, preferably at least 70%, especially at least 90%.

Further, the subject of the present invention relates to a process for preparing a pharmaceutical formulation comprising the steps:

- I) providing the composition according to the invention
- II) optionally adding further excipient(s) (c) to the composition of step I),
- III) processing the mixture of step I) or II) to a solid oral dosage form.
- IV) optionally film-coating the oral dosage form

In step I) a composition according to the present invention is provided, i.e. all the above process steps i), ii) and iii) leading to the present composition also apply to the process for preparing the pharmaceutical formulation.

- 5 In a preferred embodiment the solution or dispersion of the above-mentioned step ii) may be granulated before the solvent is removed in step iii). The resulting granules may further be processed in step II).

10 In step II) one or more further excipient(s) (c) can optionally be added to the composition of step I) or vice versa. During or after the addition of the optional excipients the mixture can preferably be blended and the resulting mixture may be preferably subjected to a granulation, such as a wet or a dry granulation.

15 Preferably, a wetted mass is formed, wherein particles are attached to each other, thereby forming larger particles. The attachments may occur through physical forces, preferably van der Waals forces. The attachment of particles preferably does not occur through chemical reactions. The wetted mass can preferably be granulated by kneading it in a mixer, preferably in a fluid or intensive mixer or in a planetary compulsory mixer and then brought into the desired particle form and
20 seize by sieving or by passing through a perforated disc device.

The resulting mixture, preferably granulates, can be dried. For drying the mixture, common dryers can be used, preferably a drying chamber, more preferably a
25 drying chamber at 30°C.

In step III) one or more further excipient(s), such as lubricant, may be added and the mixture is processed into a solid oral dosage form. Processing the mixture into a solid oral dosage form can preferably comprise manufacturing the pharmaceutical formulation into tablets or filling the formulation into capsules,
30 preferably hard gelatine capsules. Optionally, manufacturing the formulation into tablets can be carried out by compressing said formulation on a rotary press, e.g. on a Fette[®] (Fette GmbH, Germany) or a Riva[®] piccola (Riva, Argentina). If a rotary press is applied, the main compression force can range from 1 to 50 kN, preferably 3 to 40 kN. The resulting tablets can have a hardness of 30 to 400 N,
35 more preferred of 50 to 250 N, wherein the hardness can be measured according to Ph.Eur. 6.0, Chapter 2.9.8. For the optional filling of the formulation into capsules, dependent dosing systems (for example an auger) or preferably independent dosing systems (for example MG2, Matic (IMA)) can be used.

Generally, it is noted that all comments made above with respect to the pharmaceutical formulation of the present invention also apply to the process of manufacturing such a pharmaceutical formulation.

- 5 Generally, the comments given above about preferred embodiments of the tapentadol/cyclodextrin compositions also apply to the pharmaceutical formulation of the present invention.

10 A further aspect of the invention is the use of cyclodextrin for the preparation of a pharmaceutical formulation containing tapentadol base, wherein the pharmaceutical formulation has a dissolution of at least 50%, preferably at least 70%, especially at least 90% after 15 min, determined according to USP method (USP paddle apparatus, 900 ml test medium, in phosphate buffer at pH 6.8 and 37°C, 100 rpm).

15 The present invention is illustrated by the following examples.

Experimental Part

20 Analytical Methods

The compositions were examined by X-ray powder diffraction and IR-spectroscopy.

25 X-ray powder diffraction

30 The measurements were performed as follows: The samples were analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS, Karlsruhe, Germany). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized below. The raw data were analyzed with the program EVA (Bruker-AXS).

radiation	Cu K α
source	38kV/40mA
35 detector	Vantec-1
detector slit	10.39 mm
divergence slit	variable (v6)
2 θ range /°	$2 \leq 2\theta \leq 55$
step size /°	0.017

40

IR-spectroscopy

The measurements were performed on a Thermo Nicolet, Avatar 330 FT-IR with the following conditions:

5

scans:	16
scan begin:	600 cm ⁻¹
scan end:	4000 cm ⁻¹

10 Example 1

To a solution of 1.13 g β -cyclodextrin in 74 ml water 0.2 g tapentadol free base, Form B, were added at 23°C. This suspension was stirred over night. The clear solution was lyophilized and the resulting inclusion complex was amorphous (cf. Figure 1 and Figure 4).

15

Example 2

To a solution of 1.05 g α -cyclodextrin in 8 ml water 0.2 g tapentadol free base, Form B, were added at 23°C. This suspension was stirred over night. After this, the suspension was filtered and the filtrate was evaporated. The resulting white powder (1.05 g) was crystalline (cf. Figure 2 and Figure 5).

20

Example 3

To a solution of 1.13 g γ -cyclodextrin in 74 ml water a solution of 0.2 g tapentadol in 8 ml ethanol were added. The resulting solution was stirred over night at 23°C. The solution is evaporated and the resulting white solid was crystalline (cf. Figure 3 and Figure 6).

25

30

Example 4: Tapentadol 50mg (Tapentadol CD-Complex, drugload 13%)

38.46 g tapentadol composition (5.00 g tapentadol and 33.46 g γ -cyclodextrin), 0.50 g sodium lauryl sulfate, 5.54 g mannitol, 2.50g polyvinylpyrrolidone, 2.59 g sodium croscarmellose and 0.50 g colloidal silica were sieved over a sieve with mesh size of 125 μ m and mixed in a Turbula[®] T10B shaker mixer for 20 minutes. After addition of 0.41 g magnesium stearate, blending was continued for 3 minutes. The final blend was compressed on a rotary press into 15 mm oblong tablets, each containing

35

	Tapentadol composition	384.62 mg (76.16 %)
	Mannitol	55.38 mg (10.97 %)
	Sodium lauryl sulfate	5.00 mg (0.99%)
	Colloidal silica	5.00 mg (0.99 %)
5	Polyvinylpyrrolidone	25.00 mg (4.95 %)
	Sodium croscarmellose	25.90 mg (5.13 %)
	Magnesium stearate	4.10 mg (0.81 %)

Claims

1. Composition comprising:
 - 5 (a) tapentadol free base and
 - (b) cyclodextrin, wherein (a) tapentadol and (b) cyclodextrin are present in form of a complex, preferably in form of an inclusion complex.
2. Composition according to claim 1, wherein the molar ratio of tapentadol to
10 cyclodextrin is from 0.5:1 to 2:1, more preferably from 0.8:1 to 1.2:1, most preferably about 1:1.
3. Composition according to claim 1 or 2, wherein cyclodextrin is α -cyclodextrin, β -cyclodextrin, (2-hydroxypropyl)- β -cyclodextrin and/or γ -cyclo-
15 dextrin.
4. Process for producing a composition according to any one of claims 1 to 3 comprising the steps of
 - 20 a) dissolving and/or dispersing tapentadol and cyclodextrin in a solvent;
 - b) optionally homogenizing the solution or dispersion from step a); and
 - c) removing the solvent and optionally isolating the composition.
5. Process according to claim 4, wherein composition is formed in the absence
25 of excipients and/or co-solvents.
6. Process according to claim 4 or 5, wherein step b) is an ultrasonic treatment.
- 30 7. Composition obtainable by a process according to any one of claims 4 to 6.
8. Pharmaceutical formulation, preferably in form of a solid oral dosage form comprising a composition according to any one of claims 1 to 3 or 7, and optionally one or more pharmaceutical excipient(s) (c).
35
9. Pharmaceutical formulation according to claim 8, wherein the one or more excipients(s) (c) is/are selected from surfactants (c1), wicking agents (c2), fillers (c3), binders (c4), disintegrants (c5), lubricants (c6), glidants (c7) and plasticizers (c8).

10. Pharmaceutical formulation according to claim 8 or 9 comprising

20 to 300 mg tapentadol;
20 to 1400 mg cyclodextrin;
0 to 250 mg binder;
0 to 500 mg filler;
0 to 10 mg glidant;
0 to 125 mg surfactant
0 to 25 mg lubricant; and
0 to 125 mg disintegrant.

11. Pharmaceutical formulation according to any one of claims 8 to 10, wherein the pharmaceutical formulation is a tablet having a content uniformity of 95 to 105 %, a friability of less than 5 % and/or a hardness of 30 to 180 N.

12. Pharmaceutical formulation according to any one of claims 8 to 11, wherein the formulation is for immediate release.

13. Process for producing a pharmaceutical formulation according to claim 8 or 9 comprising the steps:

- I) providing the composition according to claims 1 to 3 or 7,
- II) optionally adding further excipient(s) (c) to the composition of step I),
- III) processing the mixture of step II) to a solid oral dosage form,
- IV) optionally film-coating the oral dosage form.

14. Use of cyclodextrin for the preparation of a pharmaceutical formulation containing tapentadol base, wherein the pharmaceutical formulation has a dissolution of at least 50% after 15 min determined according to USP method (USP paddle apparatus, 900 ml test medium, in phosphate buffer at pH 6.8 and 37°C, 100 rpm).

Figure 1/6

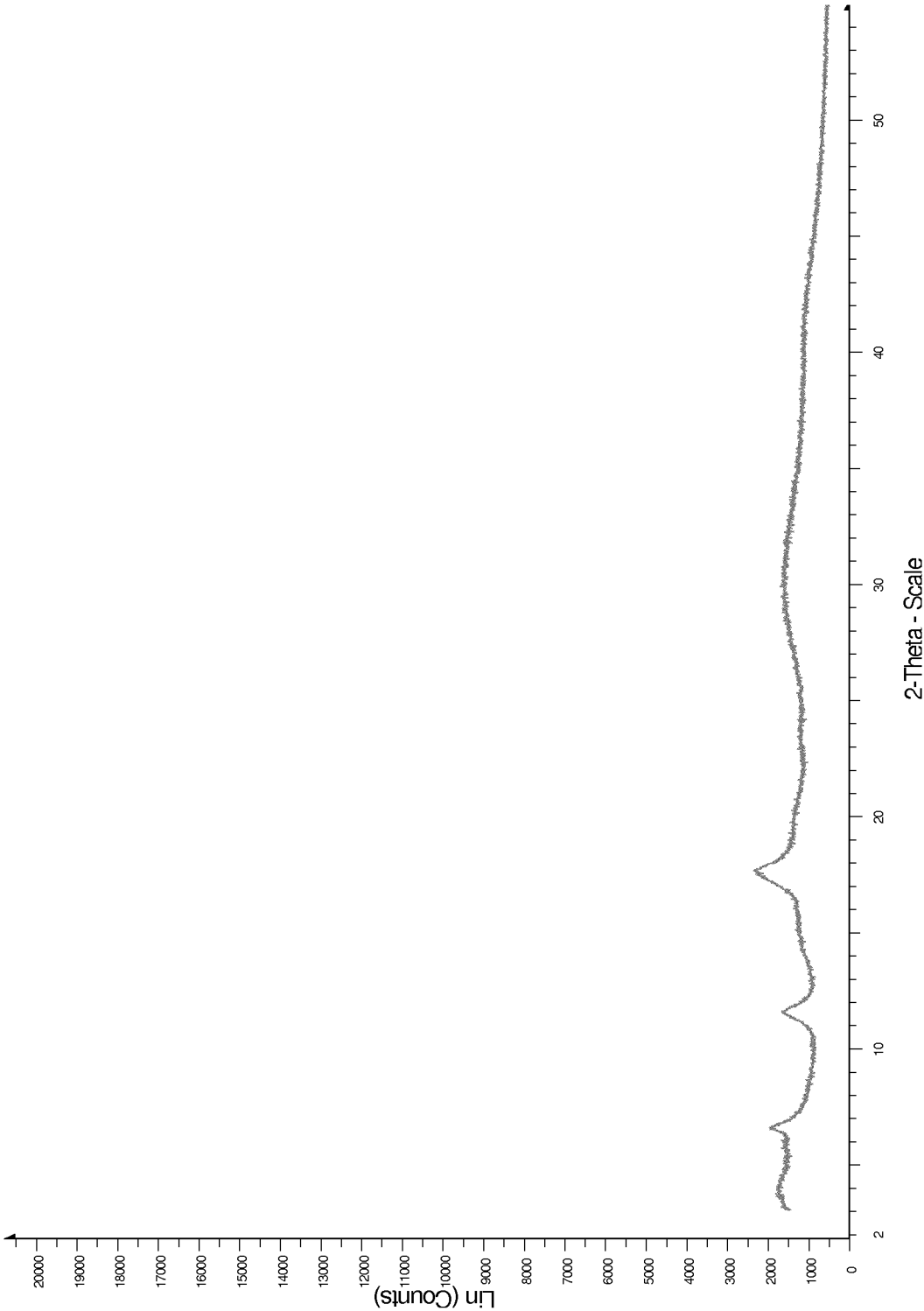


Figure A- 1 : X-Ray powder diffraction spectrum of tapentadol/ β -cyclodextrin inclusion complex after lyophilisation

Figure 2/6

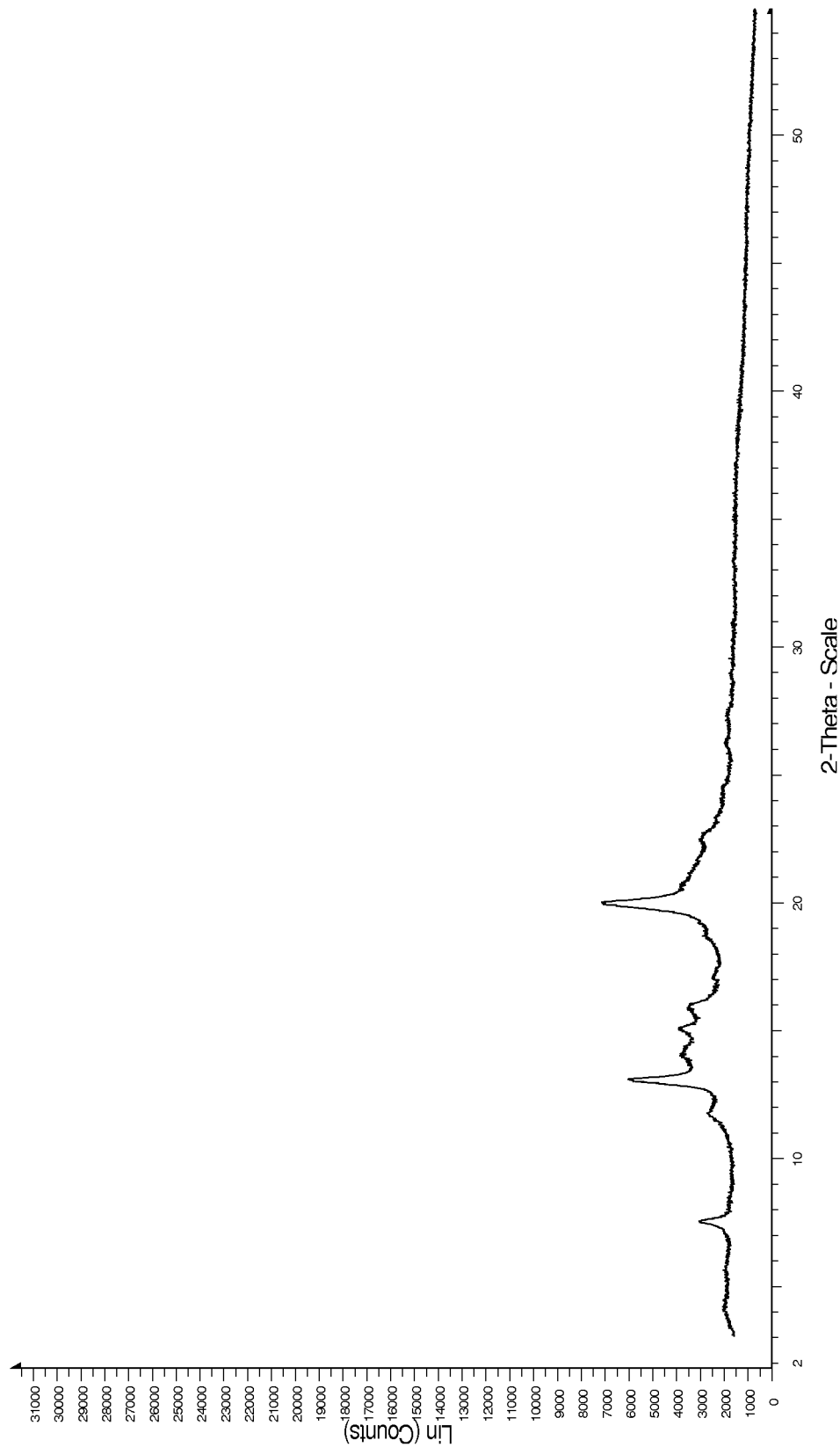


Figure A- 2 : X-Ray powder diffraction spectrum of tapentadol/ α -cyclodextrin inclusion complex

Figure 3/6

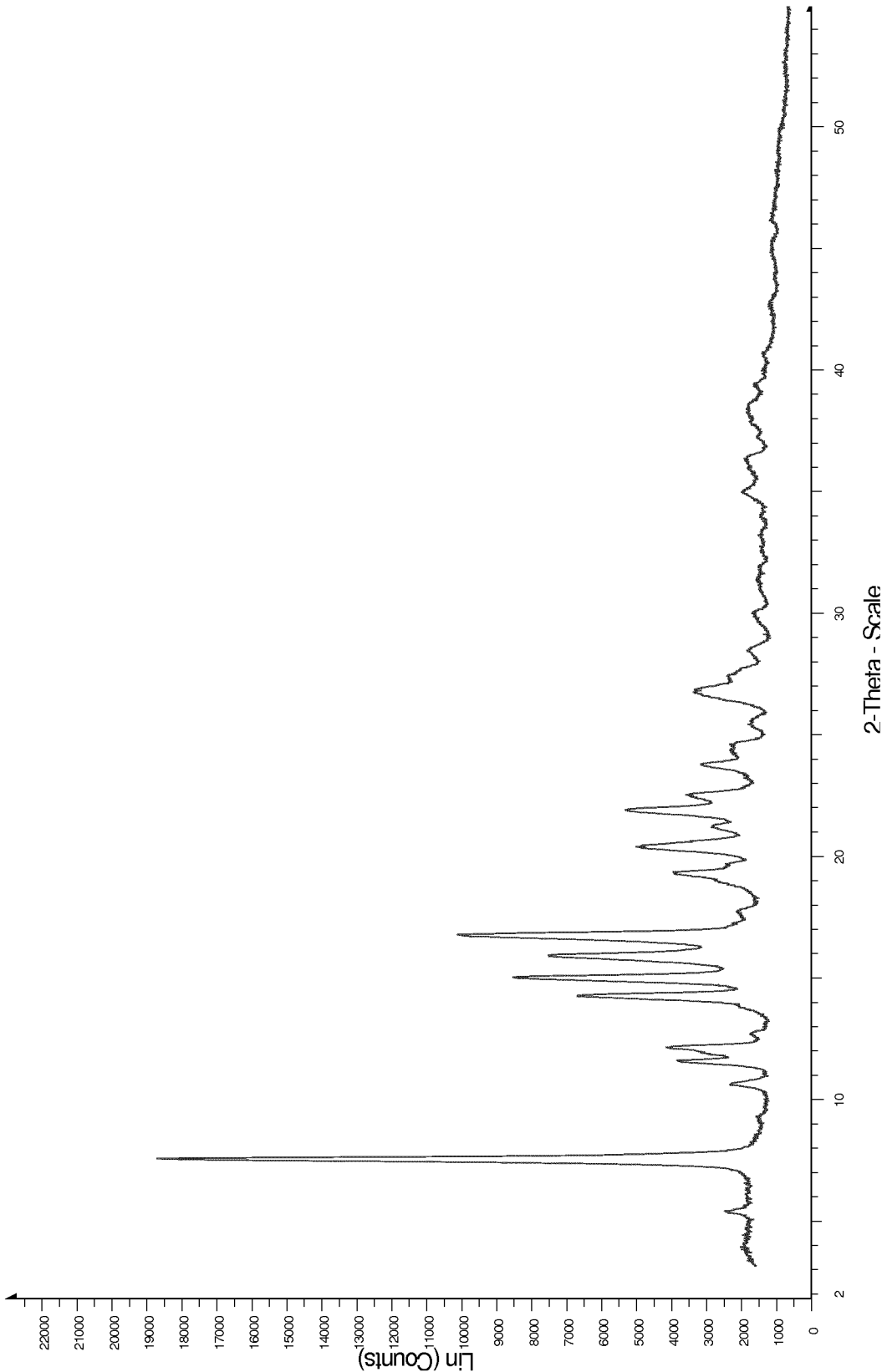


Figure A- 3 : X-Ray powder diffraction spectrum of tapentadol/ γ -cyclodextrin inclusion complex

Figure 4/6

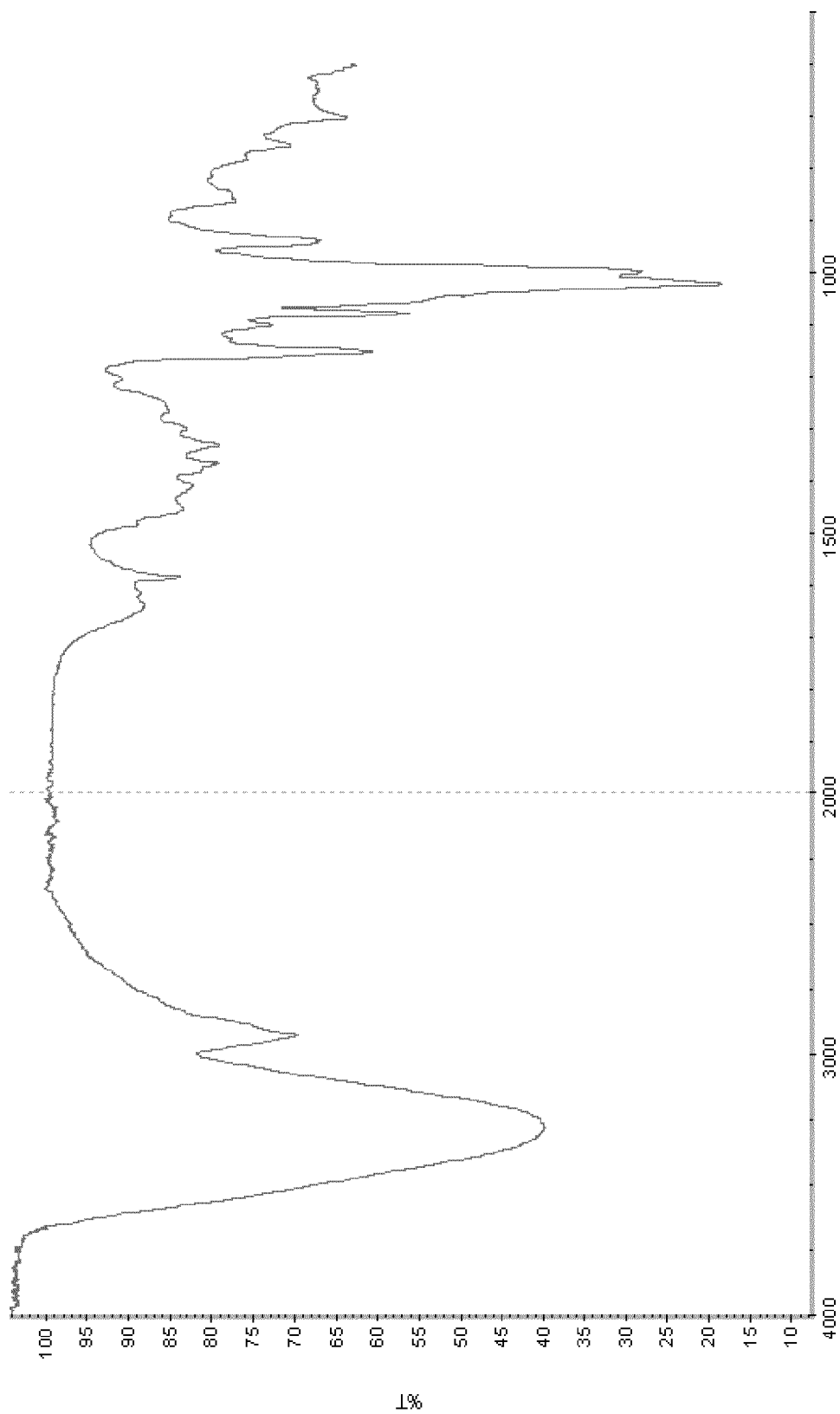
Figure A-4: FT-IR spectrum of tapentadol/ β -cyclodextrin inclusion complex with β -cyclodextrin

Figure 5/6

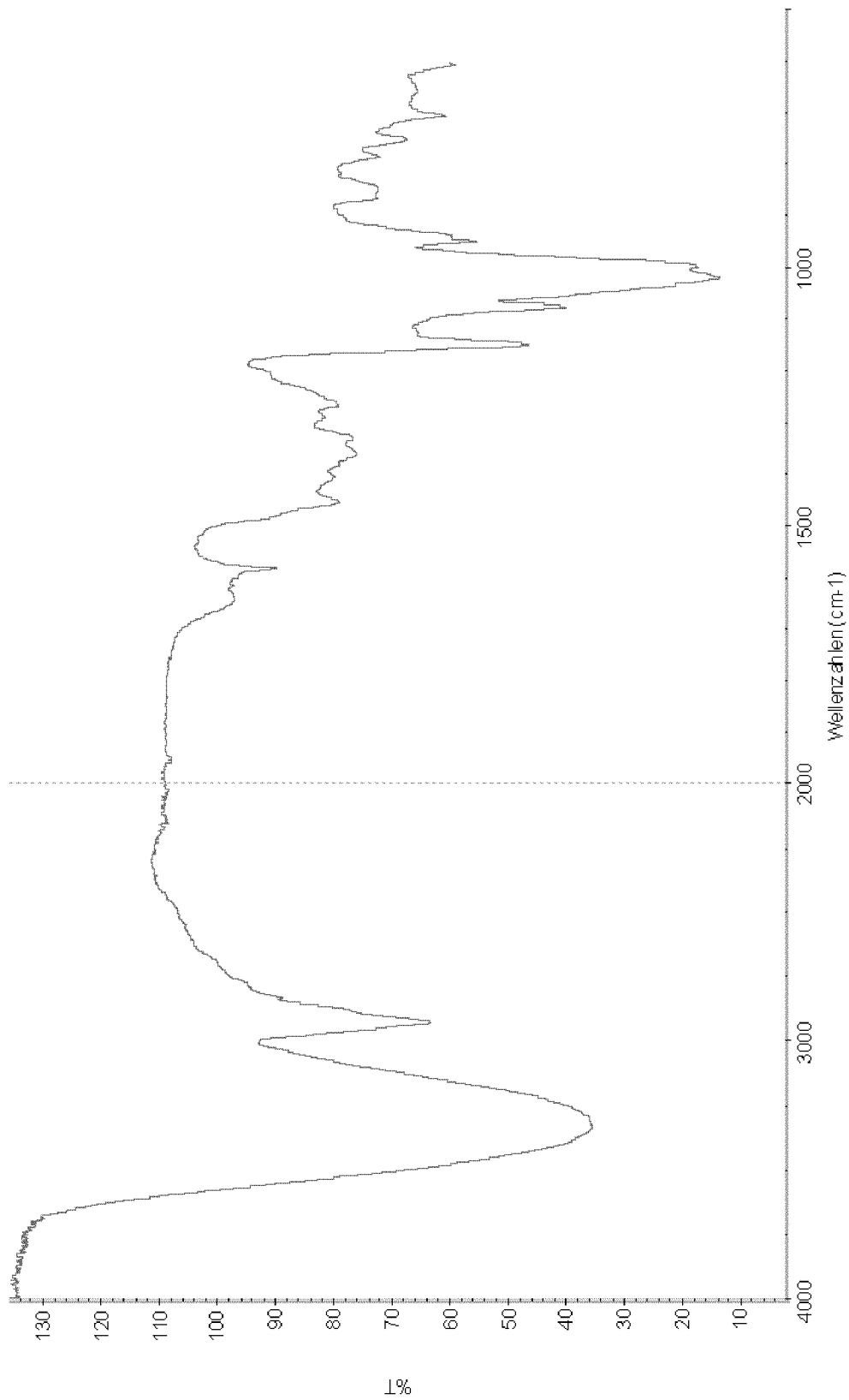
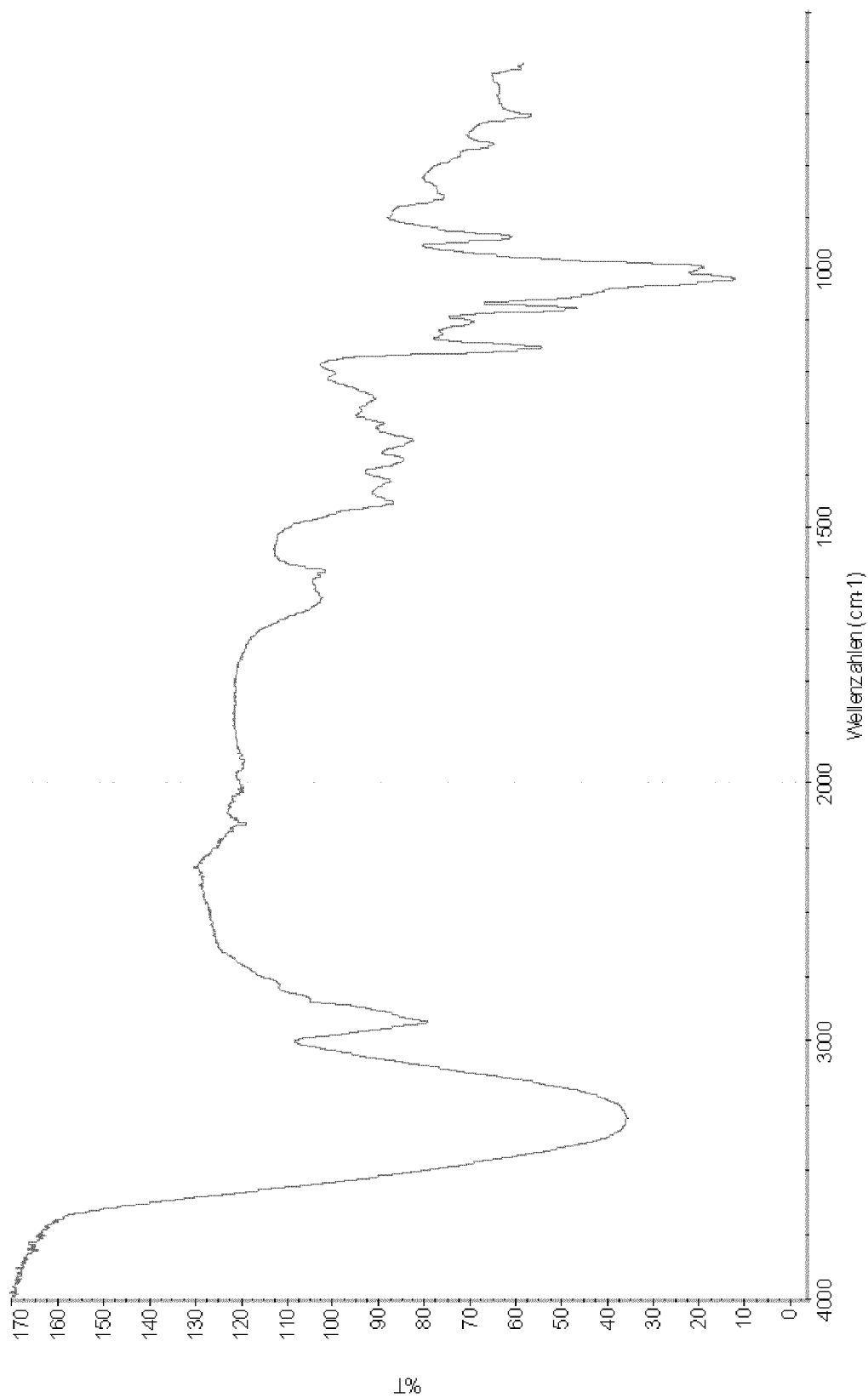
Figure A- 5: FT-IR spectrum of tapentadol/ α -cyclodextrin inclusion complex

Figure 6/6

Figure A- 6: FT-IR spectrum of tapentadol/ γ -cyclodextrin inclusion complex

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/066252

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/137 A61K9/20 A61K31/724 A61K9/28 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		
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, BIOSIS, EMBASE, SCISEARCH, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/272815 A1 (KHUNT MAYUR DEVJIBHAI [IN] ET AL) 28 October 2010 (2010-10-28)	1-14
Y	claims	1-14
Y	----- WO 2011/138037 A2 (RATIOPHARM GMBH [DE]; PAETZ JANA [DE]; STUMM DANIELA [DE]; ALBRECHT WO) 10 November 2011 (2011-11-10) page 2, line 24 - page 4, line 26; claims; examples	1-14
A	----- WO 2011/124953 A2 (LUPIN LTD [IN]; DESHMUKH ASHISH ASHOKRAO [IN]; BHUTADA PRAVIN MEGHRAJJ) 13 October 2011 (2011-10-13) claims; tables ----- -/-	1-14
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
19 September 2013	26/09/2013	
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 Venturini, Francesca	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/066252

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	----- BREWSTER ET AL: "Cyclodextrins as pharmaceutical solubilizers", ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER BV, AMSTERDAM, NL, vol. 59, no. 7, 24 August 2007 (2007-08-24), pages 645-666, XP022211985, ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2007.05.012 the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/066252

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