CO-CRYSTALLINE FORMS OF CARBAMAZEPINE

(57) Abstract: The present invention provides a novel crystalline form of a co-crystal of carbamazepine: glycolamide and of a co-crystal of carbamazepine: lactamide. The invention further provides methods for the preparation of a co-crystal of carbamazepine: glycolamide and/or carbamazepine: lactamide, as well as their use in pharmaceutical applications, in particular in medicaments for the treatment of epilepsy, bipolar disorder, schizophrenia and/or trigeminal neuralgia. The co-crystalline form of carbamazepine: glycolamide and/or carbamazepine: lactamide can be used in combination with other medicaments.
Title: Co-crystalline forms of carbamazepine

The present invention relates to novel crystalline forms of carbamazepine, in particular a co-crystal of carbamazepine with glycolamide, methods for the preparation and the formulation and application in the field of medicine, in particular medicines used for psychiatric disorders.

Carbamazepine, or 5-carbamoyl-5H-dibenz(b, f)azepine (or 5H-dibenz(b, f)azepine-5-carboxamide or N-carbamoyliminostilbene), is an iminostilbene derivative.

Carbamazepine and its synthesis are described in U.S. Pat. No. 2,948,718. Other processes for synthesising carbamazepine are described in EP 0 029 409, EP 0 277 095, EP 0 688 768, EP 0 423 679, and EP 0 485 685.

Carbamazepine, has anticonvulsant properties, which have been found useful in the treatment of psychomotor epilepsy and as an adjunct in the treatment of partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalisation of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy.

Additionally, carbamazepine is used in various psychiatric disorders such as bipolar disorder, depression, cocaine addiction, alcohol addiction, opiate addiction, nicotine addiction, other obsessive compulsive disorders, cardiovascular disease and neurological disorders such as chronic pain states and headaches. It is commercially available in the form of tablets, chewable tablets, syrups and extended release formulations sold under the brand-names Biston, Calepsin, Carbatrol, Epitol, Equestro, Finlepsin, Sirtal,
Stazepam, Tegretol, Telesmin, and Timonil. Carbamazepine relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Carbamazepine given as a monotherapy or in combination with lithium or neuroleptics has been found useful in the treatment of acute mania and the prophylactic treatment of bipolar (manic-depressive) disorders. Carbamazepine is a poorly water-soluble drug (0.11 gr/L at 25 degrees Celsius, i.e. HO ppm). Pharmacokinetic studies have shown it to be slowly and erratically absorbed from the gastro-intestinal tract when administered in tablet form. Carbamazepine is used for systemic applications, which have many disadvantages such as the need for high dosages (The regular dosage for an adult is 800-1200 mg per day, but in different cases it comes up to 1600 mg), toxicity to the organs like liver and others, side effects at unaffected tissues and long-lasting results. Carbamazepine may cause adverse haematological effects, neuropathy and hypersensitivity syndrome including dermatitis. The enhancement of its solubility leading to higher bioavailability may be crucial in decreasing the dosage and the side effects.

Currently research is directed towards the provision of forms that overcome disadvantages of carbamazepine, such a its variable dissolution rate (currently strongly depending on pH fluctuations in the stomach etc.). To this end inter alia hydroxylated forms of carbamazepine are being developed. However, although perhaps providing one solution to the issue of dissolution rate, it is also observed that these hydroxylated forms show interspecies differences with respect to metabolism, making this route less attractive.

Hence there is a need for solid forms of carbamazepine that overcome the disadvantages of the previously known forms and that avoid the necessity of complex formulation methods.

Active pharmaceutical ingredients (API or APIs (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such APIs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such APIs can also be prepared to have different physical forms. For example, the APIs may be amorphous, may have different crystalline polymorphs, or may exist in different solvation or hydration states. By varying the form of an API, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubility’s from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable
polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystalline state of an API is one of many ways in which to modulate the physical properties thereof.

It has been found that when an API and a selected co-crystal former are allowed to form co-crystals, the resulting co-crystals give rise to improved properties of the API, as compared to the API in a free form (including free acids, free bases, and zwitterions, hydrates, solvates, etc.), or an acid or base salt thereof. However, there is no possibility of predicting whether the envisaged co-crystal will form ad under what circumstances and what the characteristics of the co-crystal will be. This holds in particularly with respect to: solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, longer lasting therapeutic plasma concentration, hygroscopicity, crystallisation of amorphous compounds, decrease in form diversity (including polymorphism and crystal habit), change in morphology or crystal habit, etc. For example, a co-crystal form of an API is particularly advantageous where the original API is insoluble or sparingly soluble in water. Additionally, the co-crystal properties conferred upon the API are also useful because the bioavailability of the API can be improved and the plasma concentration and/or serum concentration of the API can be improved. This is particularly advantageous for orally-administrable formulations. Moreover, the dose response of the API can be improved, for example by increasing the maximum attainable response and/or increasing the potency of the API by increasing the biological activity per dosing equivalent. Typical notation for a co-crystal of an API and a co-crystal former is API:co-crystal former, the : depicting the existence of a co-crystal structure, as opposed to the generally used period (.) for salts and solvates.

It is hence advantageous to have new forms of these APIs that have improved properties formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase or decrease the dissolution rate of API-containing pharmaceutical
compositions in water, increase or decrease the bioavailability of orally-administered compositions, and provide a more rapid or more delayed onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster or slower, has a longer lasting therapeutic plasma concentration, and higher or lower overall exposure when compared to equivalent amounts of the API in its presently-known form. The improved properties discussed above can be altered in a way which is most beneficial to a specific API for a specific therapeutic effect. See for the effect of various crystal forms of carbamazepine on formulation behaviour and stability for instance Otsuka et al. in Chem. Pharm. Bull. 47(6), 852-856, 1999.

A co-crystal is commonly defined as a crystalline material comprised of two or more unique solids at room temperature, i.e. 20-25 degrees Celsius, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion with the exception that, if specifically stated, the API may be a liquid at room temperature. The co-crystals of the present invention comprise a co-crystal former that is preferably H-bonded to an API, but other interactions such as pi-stacking, guest-host complexation, Van Der Waals interactions etc. also may play a role in the formation of co-crystals. The co-crystal former may be bonded directly to the API or may be bonded to an additional molecule which is bound to the API. The additional molecule may be bonded to the API or bound ionically or covalently to the API. The additional molecule could also be a different API. Solvates of API compounds 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. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention. The co-crystals may also be a co-crystal between a co-crystal former and a salt of an API, but the API and the co-crystal former of the present invention are constructed or bonded together, preferably through hydrogen bonds. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and Van Der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a preferred interaction according to the present invention) whereby a non-covalent bond is formed
between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other.

Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. In another embodiment the co-crystal comprises two co-crystal formers. For purposes of the present invention, the chemical and physical properties of an API in the form of a co-crystal may be compared to a reference compound that is the same API in a different form. The reference compound may be specified as a free form, or more specifically, a free acid, free base, or zwitterion; a salt, or more specifically for example, an inorganic base addition salt such as sodium, potassium, lithium, calcium, magnesium, ammonium, aluminium salts or organic base addition salts, or an inorganic acid addition salts such as HBr, HCl, sulfuric, nitric, or phosphoric acid addition salts or an organic acid addition salt such as acetic, propionic, pyruvic, maleic, succinic, malic, malonic, fumaric, tartaric, citric, benzoic, methanesulfonic, ethanesulfonic, stearic or lactic acid addition salt; an anhydrate or hydrate of a free form or salt, or more specifically, for example, morpholine, and N-ethylpiperidine).

The ratio of API to co-crystal former may be stoichiometric or non-stoichiometric according to the present invention. For example, 1:1, 1.5 : 1, 1 : 1.5, 2 : 1 and 1 : 2 ratios of API:co-crystal former are acceptable.

Co-crystals of carbamazepine and saccharin or nicotinamide have been described for instance in US2006243831 and recently by Hickey et al., in the European Journal of Pharmaceutics and Biopharmaceutics (Dec. 2006 ahead of pub). The co-crystals were prepared by (wet) grinding. A carbamazepine:aspirine co-crystal has been described by Zaworotko and co-workers in J. Amer. Chem. Soc., 127, 16802-16803, 2005.

The present invention now provides for a novel crystalline form of carbamazepine. The present invention provides a co-crystal of carbamazepine with a compound of the formula R2HN-C(=O)-CH(OH)-R1.

Surprisingly, it has been found that the form according to the invention has a higher dissolution rate, which results in increased bioavailability, lower dosage and significant improvement of
pharmacokinetic profiles and hence provides a solution to the problems with carbamazepine outlined above.

Description of the Drawings:

**Figure 1A** illustrates the X-Ray Powder Diffraction patterns of glycolamide, carbamazepine and the co-crystal of carbamazepine:glycolamide as obtained from ethylacetate and form acetonitrile.

**Figure 1B** illustrates the DSC pattern of glycolamide, carbamazepine and the co-crystal.

**Figure 2A** illustrates the X-Ray Powder Diffraction patterns of lactamide, carbamazepine and the co-crystal of carbamazepine: lactamide as obtained from ethylacetate and form acetonitrile.

**Figure 2B** illustrates the DSC pattern of lactamide, carbamazepine and the co-crystal.

**Figure 3** illustrates a comparison between the dissolution rate of carbamazepine and carbamazepine:glycolamide co-crystal

**Figure 4** demonstrates the difference in solubility at 50% and 90% dissolution.

**Figure 5** shows some results from determination of the thermodynamic solubility of the co-crystal in comparison with carbamazepine.

Thus the invention provides a co-crystal of carbamazepine and R2HN-C(=O)-CH(OH)-R1, depicted as carbamazepine:R2HN-C(=O)-CH(OH)-R1 co-crystal. In certain embodiments, R1 and/or R2 can independently be selected from the group consisting of H, -CnH2n+1, CnHn-1, CnH2n-2, CnH2n-5, wherein n is from 1-9, including their enantiomers and racemates, due to the presence of -CH(OH)- moiety that may lead to (R)- R2HN-C(=O)-CH(OH)-R1 as well as (S)- R2HN-C(=O)-CH(OH)-R1 and racemic mixtures thereof, with R1 and R1 having the meaning as outlined herein.

In certain embodiments, R1 and/or R2 can independently be selected from the group consisting of H, C1-C6 (cyclo)alkyl, C1-C6 (cyclo)alkenyl, C5-C6 aromates such as cyclopentadienyl and benzene. The carbon atoms in R1 and/or R2 can be independently substituted, for instance with halogen, hydroxy, nitro, nitrile and or amine groups. In certain embodiments, the co-crystal former of the formula R2HN-C(=O)-CH(OH)-R1 is selected from the group consisting of glycolamide (R1, R2=H), lactamide (R1=CH3, R2=H), 2,3
dihydrosuccinamide (R1=(HO)CHC(=O)NH2), R2=H), 2-hydroxy-2-phenylacetamide (R1= Ph, R2=H), D-gluconamide (R1= (C(OH)H)3H, R2=H), 2-(1-adamantyl)-2-hydroxyacetamide (R1=adamantyl, R2=H).

Crystalline carbamazepine:glycolamide co-crystal:
Thus, in one aspect, the present invention provides a carbamazepine:glycolamide co-crystal, characterised by the selection of at least one, preferably at least two, more preferably at least three, even more preferably four X-ray powder diffraction peaks selected from the group consisting of 6.3, 15.6; 16.3 and 26.8 degrees two-theta +/- 0.3 degrees two-theta. The co-crystal is preferably a crystalline co-crystal.

In a preferred embodiment, the co-crystal of the present invention can be further characterised by the selection of at least one, preferably at least two, more preferably at least three, even more preferably at least four X-ray powder diffraction peaks selected from the group consisting of 8.8; 13.3; 18.2; 19.2; 20.0; 20.5; 22.0; 22.8; 23.8; 24.4; 29.0; and 29.5 degrees two-theta +/- 0.3 degrees two-theta. In a preferred embodiment at least five, preferably at least six and, in an increasingly preferred order, at least seven, eight, nine, ten or eleven peaks are selected from this group.

In another embodiment, the co-crystal can be characterised by the following set of XRPD peaks and, optionally, by the associated intensities:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Preferred embodiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak ID</td>
<td>Angle (2θ)</td>
</tr>
<tr>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>2</td>
<td>8.8</td>
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<td>3</td>
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</tr>
<tr>
<td>15</td>
<td>29.0</td>
</tr>
<tr>
<td>16</td>
<td>29.5</td>
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</tbody>
</table>

*For normalised intensity values: L = 0-35, M = 35-70, H = 70-100.

In another embodiment, the co-crystal can be characterised by an XRPD substantially according to Fig 1A.

In another embodiment, the co-crystal can be characterised by an DSC substantially according to Fig 1B.

In another embodiment, the co-crystal of the present invention can be characterised by DSC with a characterising peak at 147 °C. From the comparison with known XRPD data for two dihydrates and a monohydrate in the CSD, analysis, it is concluded that the solid co-crystal of the invention is anhydrous.

The present invention in one aspect relates to a method for the preparation of the co-crystal of carbamazepine:glycolamide comprising the steps of dissolving equimolar amounts of carbamazepine and glycolamide in acetonitrile, warming the mixture and crystallising carbamazepine:glycolamide by cooling the mixture.

The present invention further relates to a method for the preparation of the co-crystal of carbamazepine:glycolamide comprising the steps of dissolving equimolar amounts of carbamazepine and glycolamide in ethylacetate, warming the mixture and crystallising carbamazepine:glycolamide by cooling the mixture.

Crystalline carbamazepine:lactamide co-crystal:

Thus, in one aspect, the present invention provides a carbamazepine:lactamide co-crystal, characterised by the selection of at least one, preferably at least two, more preferably at least three, even more preferably four X-ray powder diffraction peaks selected from the group consisting of 7.9, 8.6, 15.8, 19.5, 21.0, 22.7, 24.3 and 26.8 degrees two-theta +/- 0.3 degrees two-theta. The co-crystal is preferably a crystalline co-crystal.

In a preferred embodiment at least five, preferably at least six and, in an increasingly preferred order, at least seven or eight peaks are selected from this group.
In another embodiment, the co-crystal can be characterised by the following set of XRPD peaks and, optionally, by the associated intensities:

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Preferred embodiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak ID</td>
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<tr>
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</tr>
<tr>
<td>7</td>
<td>24.3</td>
</tr>
<tr>
<td>8</td>
<td>26.8</td>
</tr>
</tbody>
</table>

*For normalised intensity values: L = 0-15, M = 15-40, H = 40-100.

In another embodiment, the co-crystal can be characterised by an XRPD substantially according to Fig 2A.

In another embodiment, the co-crystal can be characterised by an DSC substantially according to Fig 2B.

In another embodiment, the co-crystal of the present invention can be characterised by DSC with a characterising peak at 121 °C.

The present invention in one aspect relates to a method for the preparation of the co-crystal of carbamazepine: lactamide comprising the steps of dissolving equimolar amounts of carbamazepine and lactamide in acetonitrile, warming the mixture and crystallising carbamazepine: lactamide by cooling the mixture.

In another embodiment, the co-crystals of the present invention is in a substantially pure form, preferably substantially free from other amorphous, crystalline and/or polymorphic forms. In this respect, "substantially pure" relates to at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of the pure compound. In this respect, "substantially free from other amorphous, crystalline and/or polymorphic forms" means that no more than about 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% of these other amorphous, crystalline and/or polymorphic forms are present in the form according to the invention.
Pharmaceutical formulations comprising the co-crystal.

The present invention further relates to pharmaceutical formulations comprising the novel (crystalline form) of the carbamazepine:glycolamide and/or the carbamazepine:lactamide co-crystal.

Pharmaceutical formulations of the present invention contain the crystalline form according to the present invention, such as the co-crystal as disclosed herein. The invention also provides pharmaceutical compositions comprising the crystal form according to the present invention. Pharmaceutical formulations of the present invention contain the crystal form according to the present invention as active ingredient, optionally in a mixture with other crystal form(s).

The pharmaceutical formulations according to the invention, may further comprise, in addition to the co-crystal former, additional pharmaceutical active ingredients.

In addition to the active ingredient(s), the pharmaceutical formulations of the present invention may contain one or more excipients. Excipients are added to the formulation for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel(R)), micro fine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit(R)), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. Carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel(R)), hydroxypropyl methyl cellulose (e.g. Methocel(R)), liquid glucose, magnesium aluminium silicate, maltodextrin, methylcellulose, polymethacrylates, povidone
(e.g. Kollidon(R), Plasdone(R)), pregelatinized starch, sodium alginate and starch.

The dissolotion rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol(R), Primellose(R)), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon(R), Polyplasdone(R)), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab(R)) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. Flavouring agents and flavour enhancers make the dosage form more palatable to the patient. Common flavouring agents and flavour enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid. Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, the crystalline forms according to the present invention and any other solid excipients are suspended in a liquid carrier such
as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerine.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatine, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carborner, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carborner, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methylcellulose, ethylcellulose, gelatine guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste. Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxytoluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability. According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

For infections of the eye or other external tissues, e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.01 to 10% w/w (including active ingredient(s) in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base.
Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogues.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the emulsifying wax, and the wax together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include Tween8 60, Spans 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glycercyl monostearate and sodium lauryl sulphate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers.

Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.
Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is suitably present in such formulations in a concentration of 0.01 to 20%, in some embodiments 0.1 to 10%, and in others about 1.0% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerine, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for nasal or inhalational administration wherein the carrier is a solid include a powder having a particle size for example in the range 1 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc). Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents. Inhalational therapy is readily administered by metered dose inhalers.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.
Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatine and optionally contain a plasticizer such as glycerine and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art. A composition for tabletting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tabletted/compressed, or other excipients may be added prior to tabletting, such as a glidant and/or a lubricant.

A tabletting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients maybe compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tabletting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tabletting is known to those in the art with experience and skill in particular formulation challenges of direct compression tabletting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tabletting, however, they are not subjected to a final tabletting step.

Moreover, the crystalline forms according to the present invention can be formulated for administration to a mammal, preferably a human, via injection. The crystalline forms according to
the present invention may be formulated, for example, as a viscous liquid solution or suspension, preferably a clear solution, for injection. The formulation may contain solvents. Among considerations for such solvent include the solvent's physical and chemical stability at various pH levels, viscosity (which would allow for syringeability), fluidity, boiling point, miscibility and purity. Suitable solvents include alcohol USP, benzyl alcohol NF, benzyl benzoate USP and Castor oil USP. Additional substances may be added to the formulation such as buffers, solubilizers, antioxidants, among others. Allen et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Ed, 2004.

The present invention also provides pharmaceutical formulations comprising the crystalline form according to the present invention, optionally in combination with other polymorphic forms or co-crystals, to be used in a method of treatment of a mammal, preferably a human, in need thereof. A pharmaceutical composition of the present invention comprises co-crystal of carbamazepine and glycolamide and/or of carbamazepine and lactamide. The crystalline form according to the present invention may be used in a method of treatment of a mammal comprising administering to a mammal suffering from the ailments described herein before a therapeutically effective amount of such pharmaceutical composition. The invention further relates to the use of the crystalline form of the invention for the preparation of a medicament for the treatment of the ailments described herein before, in particular HIV.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the compounds of the present invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practised without departing from the scope of the invention.

Examples

Experimental conditions
X-ray Diffraction:
XRPD patterns were obtained using a T2 high-throughput XRPD set-up by Avantium technologies, The Netherlands. The plates were mounted on a Bruker GADDS diffractometer equipped with a Hi-Star area detector.
The XRPD platform was calibrated using Silver Behenate for the long d-spacings and Corundum for the short d-spacings. Data collection was carried out at room temperature using monochromatic CuK(α) radiation in the two-theta region between 1.5° and 41.5°. The diffraction pattern of each well is collected in two two-theta ranges (1.5° ≤ 2θ ≤ 21.5° for the first frame, and 19.5° ≤ 2θ ≤ 41.5° for the second) with an exposure time of 120 s for each frame. One of ordinary skill in the art understands that experimental differences may arise due to differences in instrumentation, sample preparation, or other factors. Typically XRPD data are collected with a variance of about 0.3 degrees two-theta, preferable about 0.2 degrees, more preferably 0.1 degrees, even more preferable 0.05 degrees. This has consequences for when X-ray peaks are considered overlapping.

Thermal analysis:
Melting properties were obtained from DSC thermograms, recorded with a heat flux DSC822e instrument (Mettler-Toledo GmbH, Switzerland). The DSC822e was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; delta-H(f) = 28.45 J/g). Samples were sealed in standard 40 microliter aluminium pans and heated in the DSC from 25°C to 300°C, at a heating rate of 20°C/min. Dry N₂ gas, at a flow rate of 50 ml/min, was used to purge the DSC equipment during measurement.

Mass loss due to solvent or water loss from the crystals was determined by TGA/SDTA. Monitoring of the sample weight, during heating in a TGA/SDTA851e instrument (Mettler-Toledo GmbH, Switzerland), resulted in a weight vs. temperature curve. The TGA/SDTA851e was calibrated for temperature with indium and aluminium. Samples were weighed into 100 microliter aluminium crucibles and sealed. The seals were pin-holed and the crucibles heated in the TGA from 25°C to 300°C at a heating rate of 20°C/min. Dry N₂ gas is used for purging. Melting point determinations based on DSC have a variability of +/- 2.0 degrees Celsius, preferably 1.0 degrees Celsius.

Crystallization of carbamazepine:glycolamide co-crystal on milliliter scale.
From acetonitrile:
A small quantity, about 60 mg of the starting material was placed in a HPLC vial. The solvent acetonitrile was added in small amounts to the vial containing the dry starting material at room temperature to a total volume of 1000 microliter and a concentration of about 60 mg/ml. The vial was shaken and the qualitative solubility was assessed visually. The solution was heated and maintained at 60 °C for 16 hours minutes. Subsequently, the solution was cooled at a rate of 0.1 °C/ min. Crystalline material started to form at 32 °C. The resulting solid was analysed by X-ray powder diffraction, DSC and identified as a carbamazepine:glycolamide co-crystal.

From ethylacetate:
A small quantity, about 60 mg of the starting material was placed in a HPLC vial. The solvent ethylacetate was added in small amounts to the vial containing the dry starting material at room temperature to a total volume of 1000 microliter and a concentration of about 60 mg/ml. The vial was shaken and the qualitative solubility was assessed visually. The solution was heated and maintained at 60 °C for 16 hours minutes. Subsequently, the solution was cooled at a rate of 0.1 °C/ min. Crystalline material started to form at 32 °C. The resulting solid form was analysed by X-ray powder diffraction, DSC and identified as carbamazepine:glycolamide co-crystal.

Crystallization of carbamazepine:lactamide co-crystal on milliliter scale.
From acetonitrile:
A small quantity, about 60 mg of the starting material was placed in a HPLC vial. The solvent acetonitrile was added in small amounts to the vial containing the dry starting material at room temperature to a total volume of 1000 microliter and a concentration of about 60 mg/ml. The vial was shaken and the qualitative solubility was assessed visually. The solution was heated and maintained at 60 °C for 16 hours minutes. Subsequently, the solution was cooled at a rate of 0.1 °C/ min. Crystalline material started to form at 32 °C. The resulting solid was analysed by X-ray powder diffraction, DSC and identified as a carbamazepine:lactamide co-crystal.

**Dissolution rate experiments**
The experiments were performed on a µDiss instrument from Pion.

In Figure 3, the result are shown from a set of experiments wherein about 2 mg of either carbamazepine (form III, Grezesiak et al,
Journal pharmaceutical sciences vol 92 no 11 November 2003) or a carbamazepine:glycolamide co-crystal were allowed to dissolve in various media over time. UV absorption at 284 nm was used to determine the amount of carbamazepine dissolved.

Figure 4 shows some graphical representations of the obtained dissolution data.

The following buffers were used: Buffers:

- water (undetermined pH)
- pH 1.5 (USP SGF without pepsin [0.05M sodium chloride adjusted to pH 1.5 with HCl])
- pH 3.0 (0.05M sodium chloride adjusted to pH 3.0 with HCl)
- pH 4.5 (0.05M sodium dihydrogen phosphate buffer adjusted to pH 4.5 with NaOH)
- pH 6.8 (USP SIF without pancreatin [0.05M sodium dihydrogen phosphate buffer adjusted to pH 6.8 with NaOH])
- pH 7.4 (0.05M sodium dihydrogen phosphate buffer adjusted to pH 7.4 with NaOH)

Thermodynamic solubility (Figure 5) was determined by making a saturated solution (slurry) of carbamazepine form III or the carbamazepine:glycolamide co-crystal. After 24 h a sample was taken from each vial and measured by LC-MS to determine the quantity of carbamazepine in the sample. From all experiments it was concluded that the co-crystal form was more soluble than Form III.
Claims

1. Co-crystal of carbamazepine and R2HN-C(=O)-CH(OH)-R1, wherein R1 and/or R2 can independently be selected from the group consisting of H, -CnH2n+1, CnHn, CnH2n-2, CnH2n-5, wherein n is from 1-9, including their enantiomers and racemates.

2. Co-crystal according to claim 1, wherein R1 and/or R2 can independently be selected from the group consisting of H, C1-C6 (cyclo)alkyl, C1-C6 (cyclo)alkenyl, C5-C6 aromates such as cyclopentadienyl and benzene.

3. Co-crystal according to claim 1 or 2, wherein R2HN-C(=O)-CH(OH)-R1 is selected from the group consisting of glycolamide (R1, R2=H), lactamide (R1=CH3, R2=H), 2,3 dihydrosuccinamide (R1=(HO)CHC(=O)NH2, R2=H), 2-hydroxy-2-phenylacetamide (R1=Ph, R2=H), D-gluconamide (R1= (C(OH)H)3H, R2=H), 2-(1-adamantyl)-2-hydroxyacetamide (R1=adamantyl, R2=H).

4. Co-crystal according to claims 1-3, wherein R2HN-C(=O)-CH(OH)R1 is selected from the group consisting of glycolamide (R1, R2=H) and lactamide (R1=CH3, R2=H).

5. Co-crystal of carbamazepine and glycolamide, characterised by one or more of:
   - at least one, preferably at least two, more preferably at least three, even more preferably four X-ray powder diffraction peaks selected from the group consisting of 6.3, 15.6; 16.3 and 26.8 degrees two-theta +/- 0.3 degrees two-theta;
   - DSC with a characterising peak at 147 °C.

6. Co-crystal of carbamazepine and glycolamide according to claim 1, characterised by one or more of:
   - a XRPD pattern substantially as set out in Table 1 and/or Fig. 1A;
   - a DSC substantially as set out in Fig. 1B.

7. Method for the preparation of a co-crystal of carbamazepine and glycolamide comprising the steps of mixing carbamazepine and
glycolamide with acetonitrile and/or ethylacetate, and crystallising the co-crystal by cooling the solution.

8. Co-crystal of carbamazepine and lactamide, characterised by one or more of:
   - at least one, preferably at least two, more preferably at least three, even more preferably four X-ray powder diffraction peaks selected from the group consisting of 7.9, 8.6, 15.8, 19.5, 21.0, 22.7, 24.3 and 26.8 degrees two-theta +/- 0.3 degrees two-theta;
   - DSC with a characterising peak at 121 °C.

9. Co-crystal of carbamazepine and lactamide according to claim 1, characterised by one or more of:
   - a XRPD pattern substantially as set out in Table 2 and/or Fig 2A;
   - a DSC substantially as set out in Fig 2B.

10. Method for the preparation of a co-crystal of carbamazepine and lactamide comprising the steps of mixing carbamazepine and lactamide with acetonitrile and crystallising the co-crystal by cooling the solution.

11. Pharmaceutical formulation comprising co-crystal of carbamazepine and glycolamide.

12. Pharmaceutical formulation comprising co-crystal of carbamazepine and lactamide.

13. Use of a co-crystal of carbamazepine and glycolamide as a medicament.

14. Use of a co-crystal of carbamazepine and lactamide as a medicament.

15. Use of a co-crystal of carbamazepine and glycolamide in the preparation of a medicament for the treatment of epilepsy, bipolar disorder, schizophrenia and/or trigeminal neuralgia.
16. Use of a co-crystal of carbamazepine and glycolamide in the treatment of epilepsy, bipolar disorder, schizophrenia and/or trigeminal neuralgia.

17. Use of a co-crystal of carbamazepine and glycolamide in combination with another active pharmaceutical ingredient.

18. Use of co-crystal of carbamazepine and lactamide in the preparation of a medicament for the treatment of epilepsy, bipolar disorder, schizophrenia and/or trigeminal neuralgia.

19. Use of a co-crystal of carbamazepine and lactamide in the treatment of epilepsy, bipolar disorder, schizophrenia and/or trigeminal neuralgia.

20. Use of a co-crystal of carbamazepine and lactamide in combination with another active pharmaceutical ingredient.
FIG 1A
Carbamazepine:glycolamide

Glycolamide

Carbamazepine, Form III

Co-crystal from ethyl acetate

Co-crystal from acetonitrile
FIG 2A
Carbamazepine: lactamide
Dissolution of carbamazepine and carbamazepine:glycolamide co-crystal

- Carbamazepine
- Carbamazepine:glycolamide co-crystal
B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>WO 03/074474 A (UNIV SOUTH FLORIDA [US]; UNIV MICHIGAN [US]; ZAWOROTKO MICHAEL J [US]); 12 September 2003 (2003-09-12) Paragraphs [0004], [0008], [0009]; claims; examples.</td>
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Date of the actual completion of the international search

26 May 2008

Date of mailing of the international search report

12/06/2008

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer
Weisbrod, Thomas
TABLE 1: DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2004/078163 A (TRANSFORM PHARMACEUTICALS INC [US]; UNIV SOUTH FLORIDA [US]; UNIV MICH) 16 September 2004 (2004-09-16) Claims; page 77, example 23 to page 86, example 85; tables I to IV.</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

   Although claims 16 and 19 are directed to therapeutic methods, the search has been carried out and based on the alleged effects of the compounds.

2. **☐** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- **☐** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
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