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(71)出願人　501079705
テバ　ファーマシューティカル　インダストリーズ　リミティド
イスラエル国，４９１３１　ペター－ティクバ，ピー．オー．ボックス　３１９０，バーゼル　ストリート　５
(74)代理人　100099759
弁理士　青木　篤
(74)代理人　100077517
弁理士　石田　敬
(74)代理人　100087413
弁理士　古賀　哲次
(74)代理人　100127085
弁理士　越阪部　倫子

最終頁に続く

(54)【発明の名称】オクスカルバゼピンの新しい結晶形態及びそれらの調製方法

(57)【要約】
本発明はオクスカルバゼピンの新しい結晶形態、より特別には、オクスカルバゼピンのＢ形態、Ｃ形態、Ｄ形態及びＥ形態である、を提供する。本発明はさらに、これらの形態の調製方法を提供する。Ｂ形態はトルエン及びジクロロメタン中におけるオクスカルバゼピン溶液からの溶媒の蒸発により調製される。Ｂ形態はまた、トルエン中におけるオクスカルバゼピン溶液を直ちに冷却することによっても得られる。上記同一の溶液をより遅い速度であるがそれでもかなり速く冷却することにより、Ｃ形態のオクスカルバゼピンを得る。上記同一の溶液をさらに遅い速度で冷却することにより、他の形態、Ｄ形態のオクスカルバゼピン、を得る。クロロホルムの溶媒和化合物、Ｅ形態のオクスカルバゼピンは、オクスカルバゼピンとクロロホルムの溶液を沈澱させることにより得られる。本発明はまた、オクスカルバゼピンの新しく発見された結晶形態を、従来技術のＡ形態を含む他の結晶形態へ変換させる方法を提供する。これらの変換は、外界温度で貯蔵することにより、１の特別な形態を加熱することにより又はプロトン性の溶媒で処理することにより、おこることができる。

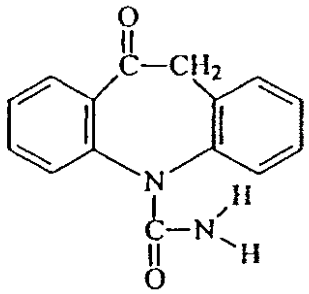
【特許請求の範囲】
【請求項１】
Ｂ形態のオクスカルバゼピン（Ｏｘｃａｒｂａｚｅｐｉｎｅ）。
【請求項２】
約１１．９、１４．４、２０．０、２３．０、２５．１±０．２度の２θにピークを有するＰＸＲＤ回折パターンを有するオクスカルバゼピン。
【請求項３】
約１１．９、１４．４、１７．７、１９．４、２０．０、２１．１、２３．０、２４．０、２４．４、２５．１、２６．０±０．２度の２θにピークを有するＰＸＲＤ回折パターンを有する、請求項２に記載の上記オクスカルバゼピン。
【請求項４】
実質的に図１に示されたＰＸＲＤ回折パターンを有する、請求項３に記載の上記オクスカルバゼピン。
【請求項５】
Ｂ形態のオクスカルバゼピンの調製方法であって、以下のステップ：
ａ）ジクロロメタン及びトルエンの混合物中におけるオクスカルバゼピン溶液の調製、及び
ｂ）残渣としてＢ形態を残す、上記トルエン及び上記ジクロロメタンの蒸発、
を含む、前記方法。
【請求項６】
上記溶液がオクスカルバゼピンをジクロロメタンに溶解し、そして上記ジクロロメタンをトルエンに加えることにより調製される、請求項５に記載の上記方法。
【請求項７】
請求項５に記載の上記方法により調製される、上記Ｂ形態のオクスカルバゼピン。
【請求項８】
Ｂ形態のオクスカルバゼピンの調製方法であって、以下のステップ：
ａ）トルエン中におけるオクスカルバゼピン溶液の調製；
ｂ）上記溶液の加熱；
ｃ）沈澱の形成をひきおこすための６０℃／分又はそれより高い速度での上記溶液の冷却；及び
ｄ）上記沈澱の分離；
を含む、前記方法。
【請求項９】
上記溶液がおよそ灌流温度まで加熱される、請求項８に記載の上記方法。
【請求項１０】
上記溶液が約０℃の温度まで冷却される、請求項８に記載の上記方法。
【請求項１１】
請求項８に記載の上記方法により調製される、上記Ｂ形態のオクスカルバゼピン。
【請求項１２】
Ｃ形態のオクスカルバゼピン。
【請求項１３】
約１１．７、２１．７、２３．２、２４．４±０．２度の２θにおけるＰＸＲＤのピークに特徴を有する、オクスカルバゼピン。
【請求項１４】
約１１．７、１７．０、１８．０、２１．７、２３．２、２４．４、２６．０±０．２度の２θにおけるＰＸＲＤのピークに特徴を有する、請求項１３に記載の上記オクスカルバゼピン。
【請求項１５】
実質的に図２に示されたＰＸＲＤ回折パターンに特徴を有する、請求項１４に記載の上記オクスカルバゼピン。

【請求項１６】
Ｃ形態のオクスカルバゼピンの調製方法であって、以下のステップ：
ａ）トルエン中におけるオクスカルバゼピン溶液の調製；
ｂ）上記溶液の加熱；
ｃ）沈澱の形成をひきおこすための約２０～６０℃／分の速度での上記溶液の冷却；
ｄ）上記沈澱の分離；
を含む、前記方法。
【請求項１７】
上記溶液が毎分約４０℃の速度で冷却される、請求項１６に記載の上記方法。
【請求項１８】
上記溶液が約０℃まで冷却される、請求項１６に記載の上記方法。
【請求項１９】
上記溶液がおよそ灌流温度まで加熱される、請求項１６に記載の上記方法。
【請求項２０】
請求項１６に記載の上記方法により調製される、上記Ｃ形態のオクスカルバゼピン。
【請求項２１】
Ｄ形態のオクスカルバゼピン。
【請求項２２】
約１１．７、１４．２、２４．３±０．２度の２θにおけるＰＸＲＤのピークに特徴を有する、オクスカルバゼピン。
【請求項２３】
実質的に図３に示されたＰＸＲＤ回折パターンに特徴を有する、請求項２２に記載の上記オクスカルバゼピン。
【請求項２４】
Ｄ形態のオクスカルバゼピンの調製方法であって、以下のステップ：
ａ）トルエン中におけるオクスカルバゼピン溶液の調製；及び
ｂ）残渣としてＤ形態のオクスカルバゼピンを残す、上記トルエンの蒸発；
を含む、前記方法。
【請求項２５】
蒸発の前に、上記溶液を加熱するステップをさらに含む、請求項２４に記載の上記方法。
【請求項２６】
上記溶液がおよそ灌流温度まで加熱される、請求項２５に記載の上記方法。
【請求項２７】
蒸発の前に、上記加熱された溶液を冷却することをさらに含む、請求項２５に記載の上記方法。
【請求項２８】
上記溶液が約０℃まで冷却される、請求項２７に記載の上記方法。
【請求項２９】
上記溶液を冷却するステップをさらに含む、請求項２４に記載の上記方法。
【請求項３０】
上記溶液が約０℃まで冷却される、請求項２９に記載の上記方法。
【請求項３１】
上記トルエンが上記溶液から蒸発により除去される、請求項２４に記載の上記方法。
【請求項３２】
請求項２４に記載の上記方法により調製される、上記Ｄ形態のオクスカルバゼピン。
【請求項３３】
オクスカルバゼピン・クロロホルム溶媒和化合物。
【請求項３４】
Ｅ形態のオクスカルバゼピン・クロロホルム溶媒和化合物。
【請求項３５】

約１４．５、１５．０、１８．２、２１．４、２２．９、２４．０、２５．８、２６．０±０．２度の２θにピークを有するＰＸＲＤパターンに特徴を有する、オクスカルバゼピン・クロロホルム溶媒和化合物。
【請求項３６】
実質的に図４に示されたＰＸＲＤ回折パターンに特徴を有する、請求項３５に記載の上記オクスカルバゼピン溶媒和化合物。
【請求項３７】
約２７重量％のクロロホルムを含む請求項３３に記載の上記オクスカルバゼピン・クロロホルム溶媒和化合物。
【請求項３８】
オクスカルバゼピン・クロロホルム溶媒和化合物の調製方法であって、以下の：
ａ）クロロホルム中におけるオクスカルバゼピン溶液からの沈澱の形成をひきおこすこと、及び
ｂ）上記沈澱の分離、
を含む、前記方法。
【請求項３９】
上記沈澱の形成をおこす前に、上記溶液を加熱するステップをさらに含む、請求項３８に記載の上記方法。
【請求項４０】
上記加熱された溶液を冷却するステップをさらに含み、ここで冷却が上記沈澱の形成をひきおこす、請求項３９に記載の上記方法。
【請求項４１】
上記溶液が約５０℃～約６０℃の高温まで加熱される、請求項３９に記載の上記方法。
【請求項４２】
上記溶液が約５５℃の高温まで加熱される、請求項４１に記載の上記方法。
【請求項４３】
上記加熱された溶液が約１０℃～約２０℃の低温まで冷却される、請求項４１に記載の上記方法。
【請求項４４】
上記低温が約１６℃である、請求項４３に記載の上記方法。
【請求項４５】
請求項３７に記載の上記方法により生産される、上記オクスカルバゼピン・クロロホルム溶媒和化合物。
【請求項４６】
Ａ形態のオクスカルバゼピンの調製方法であって、以下の：
ａ）Ｅ形態のオクスカルバゼピン・クロロホルム溶媒和化合物の供給、
ｂ）上記オクスカルバゼピン・クロロホルム溶媒和化合物の加熱、
ｃ）Ａ形態としてのオクスカルバゼピンの回収、
を含む、前記方法。
【請求項４７】
上記Ｅ形態のオクスカルバゼピン溶媒和化合物が約４０℃～約８０℃の範囲の高温まで加熱される、請求項４６に記載の上記方法。
【請求項４８】
上記高温が約６０℃である、請求項４７に記載の上記方法。
【請求項４９】
Ａ形態のオクスカルバゼピンの調製方法であって、以下の：
ａ）Ｂ形態のオクスカルバゼピンの供給、
ｂ）上記オクスカルバゼピンの加熱、及び
ｃ）Ａ形態としての上記オクスカルバゼピンの回収、
を含む、前記方法。

【請求項５０】
Ｂ形態のオクスカルバゼピンが約６０℃～約１２０℃の範囲の高温まで加熱される、請求項４９に記載の上記方法。
【請求項５１】
上記高温が約６０℃である、請求項５０に記載の上記方法。
【請求項５２】
Ｃ形態のオクスカルバゼピンの調製方法であって、以下の：
ａ）Ｂ形態のオクスカルバゼピンの供給、
ｂ）約２０℃～約３０℃の範囲の温度にオクスカルバゼピンを維持すること、
ｃ）Ｃ形態としての上記オクスカルバゼピンの回収、
を含む、前記方法。
【請求項５３】
Ａ形態のオクスカルバゼピンの調製方法であって、以下の：
ａ）Ｂ形態のオクスカルバゼピン、Ｃ形態のオクスカルバゼピン及びＤ形態のオクスカルバゼピンから成る群から選ばれたオクスカルバゼピンをプロトン性の溶媒と接触させること；及び
ｂ）Ａ形態としてのオクスカルバゼピンの回収；
を含む、前記方法。
【請求項５４】
上記形態のオクスカルバゼピンがプロトン性の溶媒に懸濁される、請求項５３に記載の上記方法。
【請求項５５】
上記プロトン性の溶媒が水及びエタノールから成る群より選ばれる、請求項５３に記載の上記方法。
【請求項５６】
上記オクスカルバゼピンが上記プロトン性の溶媒に約２時間～約３日間懸濁される、請求項５４に記載の上記方法。
【請求項５７】
上記オクスカルバゼピンが約１日間懸濁される、請求項５６に記載の上記方法。
【請求項５８】
医薬組成物であって、以下の：
ａ）Ｂ形態のオクスカルバゼピン、Ｃ形態のオクスカルバゼピン、Ｄ形態のオクスカルバゼピン及びＥ形態のオクスカルバゼピンから成る群から選ばれるオクスカルバゼピン；及び
ｂ）医薬品として許容できる賦型剤；
を含む、前記組成物。
【請求項５９】
上記組成物が１又はそれを越える形態のオクスカルバゼピンと混合される、請求項５８に記載の上記医薬組成物。
【請求項６０】
請求項５８に記載の医薬組成物を含む、医薬品の剤型。
【請求項６１】
上記剤型がカプセル又は錠剤である、請求項６０に記載の上記医薬品の剤型。
【請求項６２】
上記剤型が錠剤である、請求項６１に記載の上記医薬品の剤型。
【請求項６３】
約１５０mg～約６００mgのオクスカルバゼピンの単位用量を含む、請求項６０に記載の上記医薬品の剤型。
【請求項６４】
約１５０mg、３００mg及び６００mgから成る群から選ばれる単位用量を含む、請求項６３

に記載の上記医薬品の剤型。
【請求項６５】
上記剤型が経口懸濁液である、請求項６０に記載の上記医薬品の剤型。
【請求項６６】
上記用量が約６０$mgml^{-1}$である、請求項６５に記載の上記医薬品の剤型。
【請求項６７】
上記用量が約３００$mgml^{-1}$である、請求項６６に記載の上記医薬品の剤型。
【請求項６８】
請求項５８に記載の上記医薬組成物を投与することを含む、発作の予防又は発作の重症度を軽減する方法。
【請求項６９】
上記発作がてんかんと関連する、請求項６８に記載の上記方法。
【請求項７０】
請求項５８に記載の上記医薬組成物を投与することを含む、パーキンソン病の治療方法。
【請求項７１】
請求項５８に記載の上記医薬組成物を投与することを含む、中枢神経系の抑制方法。
【請求項７２】
上記中枢神経系が電位感受性のナトリウムチャンネルをブロックすることにより抑制される、請求項７１に記載の上記方法。
【発明の詳細な説明】
【技術分野】
【０００１】
関連する出願に対する相互参照
本出願は、３５Ｕ．Ｓ．Ｃ１．１１９（ｅ）に基づく２００１年２月１２日に出願された米国仮出願第６０／２６８，３１４号の利益を請求する。
【０００２】
本発明は、オクスカルバゼピンの新しい結晶形態及びそれらの調製方法に関する。
【背景技術】
【０００３】
以下の一般式：
【化１】



により表されるオクスカルバゼピン（１０－オクソ－１０，１１－ジヒドロ－５Ｈ－ジベンズ〔ｂ，ｆ〕アゼピン－５－カルボキサミド）は、価値のある治療的利益を有し、中枢神経系抑制剤として作用する。最近、それはてんかん治療のためのＴＲＩＬＥＰＴＡＬ（登録商標）として著名である。ＴＲＩＬＥＰＴＡＬ（登録商標）の処方情報によれば、オクスカルバゼピンの薬理学的利益は主としてオクスカルバゼピンの１０－ヒドロキシ代謝物を通して発揮される。ｉｎ　ｖｉｔｒｏの研究は、上記代謝物が電位感受性のナトリウ

ムチャンネルをブロックし、これが過剰興奮した神経の膜を安定化し、反復する神経細胞の発火を阻害し、シナプスのインパルス伝播を減少させる結果となる。これらの作用は、脳内に拡がる発作の予防に重要であると考えられる。ここに参考文献として援用される米国特許第５，６５８，９００号は、さらにパーキンソン病を治療するためのオクスカルバゼピンの使用を教示するものである。ＴＲＩＬＥＰＴＡＬ（登録商標）は、１５０mg、３００mg及び６００mgの用量単位で投与される。

【０００４】

米国特許第３，７１６，６４０号；同第４，４５２，７３８号、同第４，５５９，１７４号及び同第５，８０８，０５８号は、オクスカルバゼピンの調製方法の開示のために参考文献としてここに援用されている。

【０００５】

本発明は、開示された方法又は他の方法のいずれかにより調製されたオクスカルバゼピンの固体の物理的性質に関する。これらの性質は、上記オクスカルバゼピンが固体の形態で得られる上記条件をコントロールすることにより影響を受ける。固体の物理的性質は、例えば、製粉された固体の流動性を含む。流動性は上記物質が医薬品に加工される間の取り扱いの容易さに影響する。粉末になった組成物の粒子が互いに容易に流動しない場合、製剤の専門家は、コロイド状の２酸化シリコン、タルク、でんぷん又は３塩基リン酸カルシウムのような滑剤の使用を必要とする、錠剤又はカプセル製剤の開発のためにその事実を考慮しなければならない。

【０００６】

医薬化合物の他の重要な固体の性質は水性の液体への溶解速度である。患者の胃液中での活性成分の溶解速度は、それが経口投与された活性成分が患者の血流に到達する最高速度を課すものであるため、治療的な重要性を有することができる。溶解速度はシロップ、エリキシル及び他の液体薬物の製剤においても考慮すべき事がらである。化合物の固体の形態はその圧縮における挙動及びその貯蔵安定性にも影響することができる。

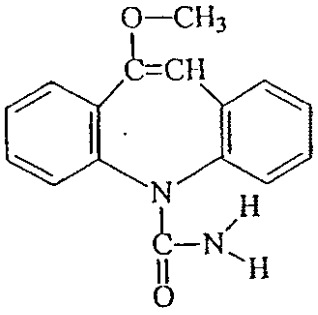
【０００７】

これらの実際的な物理的性質は、単位細胞中での分子の立体配座及び配向性により影響され、それは物質の特別な結晶形態を定義するものである。上記結晶形態は非結晶の物質又は他の多形性の形態とは異なる、熱に対する挙動を生じさせることができる。熱に対する挙動は、実験室においてキャピラリー融点、熱重量分析（ＴＧＡ）及び示差走査熱量測定（ＤＳＣ）のような技術により測定され、いくつかの多形性の形態を他から識別するのに用いられることができる。特別な多形性の形態もまた、粉末Ｘ線結晶解析、固体^{13}ＣＮＭＲ分光測定及び赤外線分光測定により検出されることができる、異なる分光学的な性質を生じさせることができる。

【０００８】

米国特許第３，７１６，６４０号によれば、オクスカルバゼピンは、以下の式：

【化２】



により表される１０－メトキシ－５Ｈ－ジベンズ〔ｂ，ｆ〕アゼピン－５－カルボキサミドから、塩酸による加水分解によって調製されることができる。エタノールからの再結晶後に融点２１５～２１６℃のオクスカルバゼピンが得られた。

【０００９】

米国特許第４，５５９，１７４号は、５－シアノ－１０－ニトロ－５Ｈ－ジベンズ〔ｂ，ｆ〕アセピン中間体を介したオクスカルバゼピンの調製方法の数多くの実施例を含む。これらの実施例中で、生成物は母液からの沈澱として得られ、いくつかの場合には再結晶され、そして他の場合には不純物を除去するために溶媒で洗浄され、又は溶媒に懸濁される。オクスカルバゼピンがそこから沈澱又は再結晶する溶媒はクロロベンゼン、酢酸／水、水、イソプロパノール、アセトニトリル及びメタノール／水である。

【００１０】

米国特許第５，８０８，０５８号は、オクスカルバゼピンが非水性の強酸の存在下での青酸ナトリウム又は青酸カリウムによる１０－メトキシミノスチルベンのＮ－カルバモイル化とそれに続く水性の弱酸によるメトキシ基の加水分解から調製されることのできることを教示する。実施例中で、オクスカルバゼピンは、ジメチルアセトアミド、シクロヘキサノン、エチルセロソルブ、２：１　ＤＭＦ：水、メタノール及びジオキサンから再結晶された。

【００１１】

商業的な製品であるＴＲＩＬＥＰＴＡＬ（登録商標）へ製剤されるオクスカルバゼピンはここでは、Ａ形態のオクスカルバゼピンと命名される。Ａ形態のオクスカルバゼピンは白からわずかにオレンジ色の結晶粉末である。それは、クロロホルム、ジクロロメタン、アセトン及びメタノールのような溶媒にわずかに可溶性であり、エタノール、エーテル及び水の溶媒には実際的に不溶である。その低い溶解性により、オクスカルバゼピンの水からの結晶化は、上記結晶化が熱い溶液から行なわれるものでない限り、実行不可能である。水並びにアセトニトリル、ＴＨＦ、酢酸エチル、エタノール／トルエン、ジクロロメタン、ＤＭＡ、ＤＭＦ、シクロヘキサン、シクロヘキサノン、アルコール、クロロホルム、水／ＤＭＡ、ＤＭＡ／ヘキサン、ＤＭＦ／エタノール、ＤＭＡ、及びアセトンのような有機溶媒からの結晶化は一貫して従来技術のＡ形態を生成する。

【００１２】

医薬品として有用な化合物の、入手可能なしかし、従来知られていない多形性の形態の発見に対する必要性がある、なぜならそれは医薬品の作用の特徴を改善する新たな機会を提供するからである。それは例えば、目的の放出プロフィール又は他の望ましい特徴を有する薬剤の医薬品としての剤型をデザインすることの可能な、製剤科学者が有する物質のレパートリーを拡大する。

【００１３】

４の新しい多形性及び偽多形性の形態のオクスカルバゼピンがここに発見された。それらは粉末Ｘ線回折（“ＰＸＲＤ”）パターン及び熱重量分析（“ＴＧＡ”）により差別化されることができる。

【００１４】

発明の要約

１の側面によれば、本発明はＢ形態のオクスカルバゼピンを提供する。他の側面によれば、本発明は約１１．９、１４．４、２０．０、２３．０、２５．１±０．２度の２θにピークを有するＰＸＲＤ回折パターンを有するオクスカルバゼピンを提供する。

他の側面によれば、本発明はジクロロメタン及びトルエンの混合物中におけるオクスカルバゼピン溶液の調製及び上記トルエン及びジクロロメタンの混合物の蒸発のステップを含むＢ形態のオクスカルバゼピンの調製方法を提供する。

他の側面によれば、本発明はトルエン中におけるオクスカルバゼピン溶液の調製、上記溶液の加熱、沈澱の形成をひき起こすための６０℃／分又はそれより高い速度での上記溶液の冷却、及び上記沈澱の分離のステップを含むＢ形態のオクスカルバゼピンの調製方法を提供する。

【００１５】
他の側面によれば、本発明はＣ形態のオクスカルバゼピンに関する。本発明は約１１．７、２１．７、２３．２、２４．４±０．２度の２θにおけるＰＸＲＤのピークに特徴を有するオクスカルバゼピンに関する。
他の側面によれば、本発明は、トルエン中におけるオクスカルバゼピン溶液の調製、上記溶液の加熱、沈澱の形成をひき起こすための約２０～６０℃／分の速度での上記溶液の冷却及び上記沈澱の分離のステップを含むＣ形態のオクスカルバゼピンの調製方法を提供する。
【００１６】
他の側面においては、本発明はＤ形態のオクスカルバゼピンに関する。本発明はまた、約１１．７、１４．２、２４．３±０．２度の２θにおけるＰＸＲＤのピークに特徴を有するオクスカルバゼピンに関する。
他の側面においては、本発明はトルエン中におけるオクスカルバゼピン溶液の調製、及びＤ形態のオクスカルバゼピン残渣を残すトルエンの蒸発のステップを含むＤ形態のオクスカルバゼピンの調製方法を提供する。
【００１７】
他の側面によれば、本発明はＥ形態のオクスカルバゼピン・クロロホルム溶媒和化合物を提供する。
他の側面によれば、本発明はオクスカルバゼピン・クロロホルム溶媒和化合物に関する。本発明はまた、約１４．５、１５．０、１８．２、２１．４、２２．９、２４．０、２５．８、２６．０±０．２度の２θにおけるＰＸＲＤピークに特徴を有するオクスカルバゼピン溶媒和化合物に関する。
【００１８】
他の側面においては、本発明はクロロホルム中のオクスカルバゼピン溶液からの沈澱の形成をひき起こすこと及び上記沈澱の分離を含む、Ｅ形態のオクスカルバゼピン・クロロホルム溶媒和化合物の調製方法を提供する。
他の側面においては、本発明はＥ形態のオクスカルバゼピン溶媒和化合物の加熱を含むＡ形態のオクスカルバゼピンの調製方法を提供する。
他の側面においては、本発明は、Ｂ形態のオクスカルバゼピンの加熱を含むＡ形態のオクスカルバゼピンの調製方法を提供する。
【００１９】
他の側面においては、本発明は、Ｂ形態のオクスカルバゼピンを外界温度で貯蔵することを含むＣ形態のオクスカルバゼピンの調製方法を提供する。
他の側面においては、本発明はＢ形態のオクスカルバゼピン、Ｃ形態のオクスカルバゼピン及びＤ形態のオクスカルバゼピンから成る群から選ばれるオクスカルバゼピンをプロトン性の溶媒と接触させることを含む、Ａ形態のオクスカルバゼピンの調製方法を提供する。
他の側面においては、本発明は、Ｂ形態のオクスカルバゼピン、Ｃ形態のオクスカルバゼピン、Ｄ形態のオクスカルバゼピン及びＥ形態のオクスカルバゼピンから成る群から選ばれるオクスカルバゼピン及び医薬品として許容できる賦型剤を含む、医薬組成物に関する。
【００２０】
発明の詳細な説明
ここで用いられるように、“溶液”という用語は、混合物を指し、それは好ましくは均一である。均一な混合物は、上記混合物をひき続き加熱することをしなければ、最初の溶質の溶媒への添加からは生じ得ない。
トルエン、トルエン：ジクロロメタン混合物及びクロロホルム中におけるオクスカルバゼピン溶液の急速な冷却又は蒸発により誘導される結晶化により得られることのできる従来技術のＡ形態と区別される新しい結晶形態が、ここに発見された。
オクスカルバゼピンの４の新規な結晶形態が単離され、特徴づけられた。これらの形態は

、それらのＰＸＲＤパターンにより区別される。上記すべてのサンプルのＤＳＣプロフィールは、約２３０℃における分解に付随する融解ピークを示す。
一般的には、ＰＸＲＤにおいては、化合物は回折ピークの位置及び強度により特徴づけられることができる。しかしながら、ピークの強度は、中でも配向効果によってサンプルごとに異なる。結晶の性質によってある回折ピークを増強し、他を減弱させる一定の配向性が好ましい。我々は以下に、我々が測定した上記サンプルにおける最大ピークを“主要な”又は“最強の”ピークと記述する。しかしながら、これらのピークは、配向効果によって、いくつかのサンプル又は調製物においては最大のピークでないかも知れない。一方、ピーク位置は配向効果によって大部分影響されない。

【００２１】

本発明は、Ｂ形態と命名されるオクスカルバゼピンの新規な形態を提供する。上記Ｂ形態のオクスカルバゼピンは、約１１．９、１４．４、２０．０、２３．０、２５．１±０．２度の２θにピークを有するＰＸＲＤパターン（図１）に特徴を有することができる。より特別には、上記Ｂ形態のオクスカルバゼピンは、約１１．９、１４．４、１７．７、１９．４、２０．０、２１．１、２３．０、２４．０、２４．４、２５．１、２６．０＋０．２度の２θにピークを有するＰＸＲＤパターンに特徴を有することができる。
Ｂ形態は、ジクロロメタン中におけるオクスカルバゼピン溶液の調製、上記溶液のトルエンへの添加及び制御された速度での上記混合溶媒の蒸発により得られることができる。オクスカルバゼピンは、好ましくは約１：６６～約１：１１６、より好ましくは１：１１０の重量比でジクロロメタンに溶解される。オクスカルバゼピンの溶解後に好ましくは約９．４mlg^{-1}ジクロロメタン～１２．８mlg^{-1}ジクロロメタン、より好ましくは約８．５mlg^{-1}の量でトルエンが加えられる。上記溶媒が毎分その最初の容量の約１／３０～約１／５０ずつ、より好ましくは毎分その最初の容量の約１／４０ずつ蒸発される場合、上記混合溶媒の蒸発の間にオクスカルバゼピンはＢ形態へ結晶化する。この蒸発速度は、フラスコをあたためずにアスピレーター吸引を伴う、慣用のロータリーエバポレーターを用いて得ることができる。好ましくは、均一な混合物が得られるようなやり方でオクスカルバゼピンがジクロロメタン中に添加される。

【００２２】

Ｂ形態はトルエン中におけるオクスカルバゼピン溶液の調製、上記溶液の加熱、沈澱の形成をひき起こすための６０℃／分又はそれより高い速度での上記溶液の冷却、及び上記沈澱の分離のステップを含む代替方法により調製されることができる。
最初にオクスカルバゼピンは、溶液を形成するために好ましくはトルエン１ｇあたり約８mg～約１０mgの比率でトルエンに添加される。上記溶液はトルエンにオクスカルバゼピンを実質的に溶解するのに十分な時間、好ましくは灌流温度まで加熱される。
上記溶液はその後非常に急速に、すなわち約６０℃／分又はそれより速い速度で、約０℃まで冷却される。そのような急速な冷却は－１３℃の温度の含塩氷浴中に上記サンプルを浸すことにより達成されることができる。上記溶液を急速に冷却することは明らかに動力学的に好ましい産物であるＢ形態のオクスカルバゼピンの形成へ導く。オクスカルバゼピンは約５分未満で上記溶液から沈澱し、その後分離される。好ましくは、Ｂ形態のオクスカルバゼピンを分離するためにフィルターが用いられる。濾過するために、上記溶液は、紙、グラスファイバー又は他の膜材料或いはセライトのような清澄剤を通されることができる。

【００２３】

本発明はまた、Ｃ形態のオクスカルバゼピンを提供する。Ｃ形態のオクスカルバゼピンは、約１１．７、２１．７、２３．２、２４．４±０．２度の２θにピークを有するＰＸＲＤパターン（図２）に特徴を有する。さらに好ましくは、Ｃ形態は約１１．７、１７．０、１８．０、２１．７、２３．２、２４．４、２６．０±０．２度の２θにおけるピークに特徴を有する。
本発明はまた、トルエン中におけるオクスカルバゼピン溶液の調製、上記溶液の加熱、沈澱の形成をひき起こすための約６０℃／分又はそれより高い速度での上記溶液の冷却及び

上記沈澱の分離のステップを含むＣ形態のオクスカルバゼピンの調製方法を提供する。
【００２４】
オクスカルバゼピンは、引き続き加熱されるところの溶液を形成するためにトルエンに添加される。好ましくは、オクスカルバゼピンは、約７．３$mgml^{-1}$～約９．０$mgml^{-1}$、より好ましくは約８．１$mgml^{-1}$の量で添加される。上記溶液は好ましくは、約２５℃～およそ灌流温度まで、最も好ましくは、灌流温度又はその近くの温度で加熱される。当業者は、上記加熱ステップの後にのみ上記溶液が完全に均一であることができることを理解しうるだろう。
約１０分間加熱した後、上記溶液はその後急速に冷却される。上記溶液はＢ形態を得るのに用いられたよりも遅いが、しかし主生産物としてＣ形態のオクスカルバゼピンの形成に備えるのに十分に速い速度で冷却される。好ましくは、上記溶液は１分あたり約２０℃～約６０℃の速度、そして最も好ましくは１分あたり約４０℃の速度で冷却される。１分あたり４０℃の速度で上記溶液を冷却するために、０℃の温度の含塩氷浴が使用されることができる。
【００２５】
上記溶液は好ましくは約０℃まで冷却される。当業者は実質的なＣ形態の形成に備える限りにおいては他の温度もまた十分であることを理解しうるだろう。冷却の後、沈澱が形成し、その後これは分離される。好ましくは、上記沈澱はフィルターにより分離される。濾過するために、上記溶液は、紙、グラスファイバー、又は他の膜材料或いはセライトのような清澄剤を通されることができる。
【００２６】
本発明はまた、Ｄ形態のオクスカルバゼピンを提供する。Ｄ形態のオクスカルバゼピンは、約１１．７、１４．２、２４．３±０．２度の２θにピークを有するＰＸＲＤパターン（図３）に特徴を有する。
本発明はトルエン中におけるオクスカルバゼピン溶液の調製、及び上記溶液からの上記トルエンの蒸発のステップを含むＤ形態のオクスカルバゼピンの調製方法を提供する。
最初にオクスカルバゼピンが溶液を形成するためにトルエンに添加される。好ましくは、オクスカルバゼピンは、トルエン１グラムあたり約８．５～約９．５ミリグラム、より好ましくは約９．１mgg^{-1}の量で添加される。
上記溶液はその後、上記オクスカルバゼピンを完全に溶解するために好ましくは加熱される。上記溶液は温度及び時間が相違しても同一の結果を達成できるにもかかわらず、好ましくは、短時間、約５分間、灌流される。
【００２７】
加熱の後、上記溶液は好ましくは、上記トルエン中のオクスカルバゼピンの溶解度を減少させるために冷却される。上記溶液は、Ｂ形態及びＣ形態において得られた方法よりも遅い速度で冷却される。上記溶液は２０℃／分及びそれより低い速度、より好ましくは約１０℃／分～２０℃／分の速度で、そして最も好ましくは１５℃／分の速度で冷却される。
上記溶液は、冷却の間に沈澱が実質的に形成しないような方法で冷却される。
上記溶液は好ましくは約０℃～およそ室温まで、最も好ましくは約０℃まで冷却される。当業者は、他の温度も同一の結果を達成できることを理解しうるだろう。
冷却後、上記トルエンは蒸発により除去される。上記トルエンは、外界温度下又は減圧下で蒸発させられることができ、場合により蒸発を促進するために加熱されることができる。蒸発の後ＰＸＲＤ分析で確認した、残った残渣はＤ形態のオクスカルバゼピンである。
【００２８】
実施例１中のＢ形態の調製方法とＤ形態の調製方法は類似している。Ｄ形態を調製するために、オクスカルバゼピンは最初にトルエンに添加され、その後上記トルエンが蒸発させられる。Ｂ形態を調製するために、オクスカルバゼピンは最初にジクロロメタンに溶解され、そしてトルエンに溶液として添加される。上記混合溶媒はその後、Ｂ形態を得るために蒸発により除去される。
【００２９】

本発明はまたクロロホルム溶媒和化合物としてのオクスカルバゼピンを提供する。本発明のオクスカルバゼピン溶媒和化合物は、約１４．５、１５．０、１８．２、２１．４、２２．９、２４．０、２５．８、２６．０±０．２度の２θにピークを有するＰＸＲＤパターン（図４）に特徴を有する。さらに特別には、本発明はＥ形態のオクスカルバゼピン・クロロホルム溶媒和化合物を提供する。
この形態は約２７％の溶媒を含み、それはクロロホルムの３／４溶媒和化合物にあたる。上記溶媒含量はＴＧＡにより測定され、３０℃及び９０℃の間で２７％の重量減少が見られた。この脱溶媒和はＤＳＣにおいても約４０℃～９０℃の温度範囲における吸熱量として観察される。

【００３０】

本発明はまた、クロロホルム中におけるオクスカルバゼピン溶液からの沈澱の形成、及び上記沈澱の分離を含むＥ形態のオクスカルバゼピン溶媒和化合物の調製方法を提供する。使用された条件は、例えば灌流温度における溶解及び１０℃／分の速度での冷却である、クロロホルムからの結晶化による形態Ａの生産の条件とは異なる。
オクスカルバゼピンは、溶液を形成するために最初はクロロホルムに溶解される。オクスカルバゼピンは、好ましくはクロロホルム１グラムあたり約６．８～約８．０ミリグラム、さらに好ましくは約７．３mgg^{-1}の量で添加される。上記溶液はその後、上記クロロホルムにより吸収されるオクスカルバゼピンの量を増加させるために、好ましくは加熱される。好ましくは、上記加熱ステップの後、上記溶液は完全に均一である。上記溶液は好ましくは約５０℃～約６０℃、そして最も好ましくは約５５℃まで加熱される。
加熱後、上記溶液は冷却される。好ましくは、上記溶液は室温又は室温未満まで冷却される。最も好ましくは、上記溶液は約１６℃まで冷却される。上記溶液が冷却されると、オクスカルバゼピンのクロロホルムに対する溶解度は減少する。未熟な沈澱を伴わないで、上記溶液を約１６℃の低温まで冷却させるには、上記溶液は最初に第１の温度まで冷却され、しばらく後に第２のより低い温度まで冷却される。好ましくは、上記溶液は最初に約２５℃まで冷却され、その後室温未満まで冷却される。冷却後、沈澱が形成する。上記沈澱はフィルターを用いて分離されることができる。濾過の前に、上記溶液は温まるために放置されることができる。好ましくは、上記溶液は約２５℃まで温められる。

【００３１】

本発明はまた、１の形態のオクスカルバゼピンを他の形態のオクスカルバゼピンに変換する方法を提供する。Ａ形態はＥ形態のオクスカルバゼピン溶媒和化合物を、４０℃及び８０℃の間の高温で、好ましくは６０℃で、２時間～１０時間、好ましくは４時間の間、加熱することにより得られることができる。当業者は、異なる条件下でＥ形態がＡ形態に変換できること、そして上記最適条件が日常的な実験法により発見されることができることを理解しうるだろう。

【００３２】

本発明は、また、Ｂ形態のＣ形態への変換方法を提供する。約２０～約３０℃において、すなわちおよそ室温において、Ｂ形態がＣ形態に変換することが発見された。上記変換は漸進的であり、時間が長引くものであって、数ヵ月を越えておこることができる。当業者は変換のための上記最適条件及び時間が日常的な実験法を通じて発見されることができることを理解しうるだろう。

【００３３】

本発明はまた、Ｂ形態のＡ形態への変換方法を提供する。およそ外界温度において、Ｂ形態はＣ形態へ変換する。当業者は、そのような転移は外界温度よりも高い又は低い温度でも起こることができること、及び日常の実験方法によって上記温度範囲の境界が決定されることができることを理解しうるだろう。６０℃及び１２０℃の間のさらに高い温度、好ましくは６０℃において、上記温度により決定される通り、２，３時間後にＢ形態からＡ形態への転移が起こる。Ｂ形態がＣ形態よりもＡ形態へ変換する上記温度は、日常の実験方法により決定されることができる。当業者は、上記変換の速度及び程度が上記変換のおこる条件及び時間量によって変わることを認識することができる。

本発明はまた、Ｂ形態、Ｃ形態及びＤ形態のＡ形態への変換方法を提供する。エタノール又は水のようなプロトン性の溶媒に数時間及び数日の間の期間、好ましくは２４時間の期間、懸濁することによってＢ形態、Ｃ形態又はＤ形態が上記従来技術のＡ形態へ直ちに変換できることが発見された。当業者は他のプロトン性の溶媒が使用されることができること及び上記最適条件が日常の実験方法を通じて決定されることができることを理解しうる。

【００３４】

本発明の上記医薬組成物は価値のある治療的利益を有し、中枢神経系抑制剤として作用する。本発明の医薬組成物は、発作を予防すること又は発作の程度を減少させることにより、てんかんの治療の使用に用いられることができる。上記組成物の薬理学的利益は主にオクスカルバゼピンの１０－モノヒドロキシ代謝物を通じて発揮される。ｉｎ ｖｉｔｒｏでの研究は、上記代謝物が電位感受性のナトリウムチャンネルをブロックし、これが過剰興奮した神経の膜を安定化し、反復する神経細胞の発火を阻害し、シナプスのインパルス伝播を減少させる結果となることを示唆する。本発明の上記医薬組成物はまたパーキンソン病を治療するために用いられる。

本発明の医薬組成物はＢ形態、Ｃ形態、Ｄ形態及び／又はＥ形態のオクスカルバゼピン、場合により他の形態との混合物で、或いは非結晶のオクスカルバゼピン及び／又は活性成分を含む。活性成分に加えて、本発明の医薬組成物は１又はそれを越える賦型剤を含むことができる。賦型剤は、多様な目的のために上記組成物に添加される。

【００３５】

希釈剤は固体の医薬組成物のバルクを増加し、上記組成物を含む医薬品の剤型を患者及び介護者にとって扱い易くする。固体の組成物のための希釈剤は、例えば、微結晶性のセルロース（例えばＡｖｉｃｅｌ（登録商標））、超微粒のセルロース、ラクトース、でんぷん、アルファ化でんぷん、炭酸カルシウム、硫酸カルシウム、糖、デキストレート、デキストリン、デキストロース、２塩基リン酸カルシウム２水和物、３塩基リン酸カルシウム、カオリン、炭酸マグネシウム、酸化マグネシウム、マルトデキストリン、マンニトール、ポリメタクリレート（例えばＥｕｄｒａｇｉｔ（登録商標））、塩化カリウム、粉末セルロース、塩化ナトリウム、ソルビトール、及びタルクを含む。

【００３６】

錠剤のような剤型に圧縮された固体の医薬組成物は、上記活性成分と他の賦型剤を圧縮の後に結合させることを補助することをその機能に含む賦型剤を含むことができる。固体の医薬組成物のための結合剤は、アラビアゴム、アルギン酸、カルボマー（例えばカルボポール）、カルボキシメチルセルロースナトリウム、デキストリン、エチルセルロース、ゼラチン、グアールゴム、水素化植物油、ヒドロキシエチルセルロース、ヒドロキシプロピルセルロース（例えばＫｌｕｃｅｌ（登録商標））、ヒドロキシプロピルメチルセルロース（例えばＭｅｔｈｏｃｅｌ（登録商標））、液体グルコース、ケイ酸マグネシウムアルミニウム、マルトデキストリン、メチルセルロース、ポリメタクリレート、ポビドン（例えばＫｏｌｌｉｄｏｎ（登録商標）、Ｐｌａｓｄｏｎｅ（登録商標））、アルファ化でんぷん、アルギン酸ナトリウム及びでんぷんを含む。

圧縮された固体の医薬組成物の患者の胃の中における溶解速度は、上記組成物への崩壊剤の添加により増大させられることができる。崩壊剤はアルギン酸、カルボキシメチルセルロースカルシウム、カルボキシメチルセルロースナトリウム（例えばＡｃ－Ｄｉ－Ｓｏｌ（登録商標）、Ｐｒｉｍｅｌｌｏｓｅ（登録商標））、コロイド状の２酸化シリコン、クロスカルメロースナトリウム、クロスポビドン（例えばＫｏｌｌｉｄｏｎ（登録商標）、Ｐｏｌｙｐｌａｓｄｏｎｅ（登録商標））、グアールゴム、ケイ酸マグネシウムアルミニウム、メチルセルロース、微結晶性のセルロース、ｐｏｌａｃｒｉｌｉｎ ｐｏｔａｓｓｉｕｍ、粉末セルロース、アルファ化でんぷん、アルギン酸ナトリウム、ソディウムスターチグリコレート（例えばＥｘｐｌｏｔａｂ（登録商標））及びでんぷんを含む。

滑剤は圧縮されていない固体組成物の流動性を亢進し、投薬の正確さを向上させるために添加されることができる。滑剤として機能する賦型剤はコロイド状の２酸化シリコン、３

ケイ酸マグネシウム、粉末セルロース、でんぷん、タルク及び３塩基リン酸カルシウムを含む。

【００３７】

錠剤のような剤型が粉末の組成物の圧縮により製造された場合、上記組成物はパンチとダイからの圧力を受ける。いくつかの賦型剤と活性成分は、パンチとダイの表面に付着する傾向があり、それは上記製品が圧痕及び他の表面の異常を有する原因となる。付着を減少させ、ダイからの上記製品の放出を容易にするために、潤滑剤が上記組成物に添加されることができる。潤滑剤はステアリン酸マグネシウム、ステアリン酸カルシウム、グリセリルモノステアレート、グリセリルパルミトステアレート、水素化ヒマシ油、水素化植物油、鉱油、ポリエチレングリコール、安息香酸ナトリウム、ラウリル硫酸ナトリウム、ステアリルフマル酸ナトリウム、ステアリン酸、タルク及びステアリン酸亜鉛を含む。

矯味剤及び矯味増強剤は剤型を患者にとってより好ましいものとする。本発明の組成物に含まれることのできる、医薬品のための通常の矯味剤及び矯味増強剤はマルトール、バニリン、エチルバニリン、メンソール、クエン酸、フマル酸、エチルマルトール及び酒石酸を含む。

固体の及び液体の組成物はまた、それらの外観を向上させ及び／又は患者が上記製品及び単位用量レベルを識別するの容易にするために、医薬品として許容できるいずれかの着色剤を用いて着色されることができる。

本発明の液体の医薬組成物中では、ｃｌｏｐｉｄｏｇｒｅｌ硫化水素塩及び他のいずれかの固体の賦型剤は、水、植物油、アルコール、ポリエチレングリコール、プロピレングリコール又はグリセリンのような液体の担体に溶解又は懸濁される。

【００３８】

液体の医薬組成物は、活性成分又は他の賦型剤であって液体の担体に不溶のものを組成物全体に均一に分散させるために乳化剤を含むことができる。本発明の液体の組成物中で有用であることができる乳化剤は、例えば、ゼラチン、卵黄、カゼイン、コレステロール、アラビアゴム、トラガカント、ツノマタ、ペクチン、メチルセルロース、カルボマー、セトステアリルアルコール及びセチルアルコールを含む。

本発明の液体の医薬組成物はまた、製品の口あたり及び／又は消化管の内側をコートするために粘度増強剤を含むことができる。そのような剤はアラビアゴム、アルギン酸ベントナイト、カルボマー、カルボキシメチルセルロースカルシウム若しくはナトリウム、セトステアリルアルコール、メチルセルロース、エチルセルロース、ゼラチン、グアールゴム、ヒドロキシエチルセルロース、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、マルトデキストリン、ポリビニルアルコール、ポビドン、プロピレンカーボネート、プロピレングリコールアルギネート、アルギン酸ナトリウム、ソディウムスターチグリコレート、スターチトラガカント及びキサンタンゴムを含む。

ソルビトール、サッカリン、サッカリンナトリウム、ショ糖、アスパルテーム、フルクトース、マンニトール及び転化糖のような甘味料は、食味を向上させるために添加されることができる。

アルコール、安息香酸ナトリウム、ブチル化ヒドロキシトルエン、ブチル化ヒドロキシアニソール及びエチレンジアミン５酢酸のような保存剤及びキレート剤は、貯蔵安定性を向上させるために摂取に安全なレベルで添加されることができる。

【００３９】

本発明によれば、液体の組成物はまた、グルコン酸、乳酸、クエン酸若しくは酢酸、グルコン酸ナトリウム、乳酸ナトリウム、クエン酸ナトリウム、酢酸ナトリウムのような緩衝液を含むことができる。

賦型剤の選択及び使用量は、経験及び上記分野における標準的な手順と参考文献を考慮することに基いて、製剤学者によって容易に決定されることができる。

【００４０】

本発明の固体の組成物は、粉末、顆粒、凝集体及び圧縮された組成物を含む。用量は経口の、舌下の、直腸の、非経口の（皮下的、筋肉内及び静脈内を含む）、吸入の及び点眼の

投与に好適な用量を含む。いかなる所定の場合においても、最適の投与方法は治療される症状の性質及び重篤度に依存するにもかかわらず、本発明の最も好ましい経路は経口である。上記用量は、単位用量で簡便に提示され、そして医薬品の分野で周知の方法のいずれかを用いて調製されることができる。
剤型は、液体シロップ、懸濁剤及びエリキシルと同様に、錠剤、散剤、カプセル、分包、トローチ及びロゼンジのような固体の剤型を含む。
本発明の剤型は、好ましくは、硬質の又は軟質の殻中の粉末の又は顆粒状の本発明の固体の組成物である、上記組成物を含むカプセルであることができる。上記殻は、ゼラチンから作られ、そして場合によりグリセリン及びソルビトールのような可塑剤、並びに乳白剤又は着色剤を含むことができる。
上記活性成分及び賦型剤はその分野における周知な方法によって、組成物そして剤型に製剤されることができる。
【００４１】
錠剤の組成物は、簡便に、乾燥混合法によって調製されることができる。例えば、活性成分と賦型剤の混合された組成物は、スラッグ又はシートに圧縮され、その後圧縮された顆粒に変えられる。上記圧縮された顆粒は、引き続き錠剤へ圧縮される。
乾式の顆粒化の代わりに、混合された組成物は、直接圧縮技術を用いて直接的に圧縮された剤型に圧縮されることができる。直接的な圧縮は顆粒を含まない、より均一な錠剤を作り出す。直接的な圧縮による錠剤化に特別によく適した賦型剤は微結晶性のセルロース、スプレー乾燥乳糖、リン酸２カルシウム２水和物、及びコロイド状のシリカを含む。直接的な圧縮による錠剤化におけるこれらの及び他の賦型剤の適切な使用は、直接的な圧縮による錠剤化の特別な製剤の挑戦において経験と技術を有する当業者に既知である。
本発明のカプセルの充填物は、錠剤化に関して、記載された前述の混合物及び顆粒のいずれかを含むことができ、それらは最終的な錠剤化のステップのみに供されるものではない。
【００４２】
本発明の固体の単位用量は、好ましくは約１５０、３００又は６００mgのオクスカルバゼピンを含む。ここで用いられる上記単位用量は、錠剤又はカプセルのような投与のビヒクルに含まれる多様な形態のオクスカルバゼピンの量を示す。最も好ましくは、本発明の単位用量は錠剤として投与される。
本発明の錠剤は、好ましくはフィルムでコートされ、そして以下の不活性成分：コロイド状の２酸化シリコン；クロスポビドン；ヒドロキシプロピルメチルセルロース；ステアリン酸マグネシウム；微結晶性のセルロース；ポリエチレングリコール；タルク及び２酸化チタニウム；黄色酸化鉄を含む。
本発明の液の単位用量は５mLの液体に懸濁した約３００mgのオクスカルバゼピンを含む。最も好ましくは、上記懸濁液は、経口で投与され、液体１ミリリッターあたり約６０mgのオクスカルバゼピンを有する。
【００４３】
本発明の上記経口懸濁液は好ましくは以下の不活性成分：アスコルビン酸；分散可能なセルロース；エタノール；ステアリン酸マクロゴール；メチルパラヒドロキシ安息香酸；プロピレングリコール；プロピルパラヒドロキシ安息香酸；精製水；サッカリンナトリウム；ソルビン酸；ソルビトール；黄色－プラム－レモン香料を含む。
結晶相の性質決定は、Ｐｈｉｌｌｉｐｓ ＰＷ １７１０ Ｄｉｆｆｒａｃｔｏｍｅｔｅｒを用いて実施された。熱重量分析（ＴＧＡ）は、Ｍｅｔｔｌｅｒ ＴＣ１１ ＴＡプロセッサーを装備したＭｅｔｔｌｅｒ ＴＧ５０を用いて行なった。示差走査熱量測定（ＤＳＣ）はＭｅｔｔｌｅｒ ＤＳＣ３０装置を用いて実施された。ＦＴＩＲスペクトルはＮｉｃｏｌｅｔ Ａｖａｔａｒ ３６０分光計を用いて記録された。
当業者は、他の単位用量も必要に応じて慣用のやり方で作られることができることを理解しうるだろう。
【実施例】

【００４４】
実施例１
Ｂ形態の調製
オクスカルバゼピン（０．１５ｇ）を室温でジクロロメタン（２０ｇ）に溶解した。完全に溶解した後、上記溶液をトルエン（１７０mL）に加えた。５分間撹拌後、上記溶媒を５ｇ／分の速度で乾燥するまで蒸発させた。得られた物質をＰＸＲＤで分析し、Ｂ形態であることがわかった。
実施例２
Ｂ形態の調製
オクスカルバゼピン（０．３ｇ）を室温でトルエン（３３ｇ）に溶解した。５分間灌流した後、上記反応混合物を直ちに０℃に冷却した。５分後、上記懸濁液を減圧下で濾過した。得られた物質をＰＸＲＤで分析し、Ｂ形態であることがわかった。
実施例３
Ｃ形態の調製
オクスカルバゼピン（０．３ｇ）を室温でトルエン（３３ｇ）に溶解した。１０分間灌流した後、上記反応混合物を４０℃／分の速度で０℃まで冷却した。５分後、上記懸濁液を減圧下で濾過した。得られた物質をＰＸＲＤで分析し、Ｃ形態であることがわかった。
【００４５】
実施例４
Ｄ形態の調製
オクスカルバゼピン（０．３ｇ）を室温でトルエン（３３ｇ）に溶解した。５分間灌流した後、上記反応混合物を０℃まで冷却した。５分後、上記溶媒を蒸発させた。得られた物質をＰＸＲＤで分析し、Ｄ形態であることがわかった。
実施例５
Ｅ形態の溶媒和化合物の調製
オクスカルバゼピン（１．１ｇ）を室温でクロロホルム（１５０ｇ）に溶解した。約５５℃まで５分間加熱後、上記反応混合物を２１．５℃まで冷却し、８時間後、上記反応混合物を１６℃まで冷却した。４８時間後、上記懸濁液を２５℃まで加熱し、減圧下で濾過した。得られた物質をＰＸＲＤで分析し、溶媒和させられたＥ形態であることがわかった。
実施例６
Ｅ形態からのＡ形態の調製
Ｅ形態のオクスカルバゼピンの溶媒和化合物を６０℃の温度まで加熱し、その温度で４時間維持した。得られた物質をＰＸＲＤで分析し、それはＡ形態のオクスカルバゼピンであることを示した。
【００４６】
実施例７
Ｂ形態からのＡ形態の調製
Ｂ形態のオクスカルバゼピンを約６０℃の温度まで加熱し、その温度で５時間維持した。得られた物質をＰＸＲＤで分析し、それはオクスカルバゼピンのＡ形態であることを示した。
実施例８
Ｂ形態からのＡ形態の調製
Ｂ形態のオクスカルバゼピンを２４時間、エタノールに懸濁した。生成物をＰＸＲＤにより分析し、Ａ形態であると決定した。
実施例９
Ｃ形態からのＡ形態の調製
Ｃ形態のオクスカルバゼピンを２４時間、エタノールに懸濁した。生成物をＰＸＲＤにより分析し、Ａ形態であると決定した。
【００４７】
実施例１０

D形態からのA形態の調製

D形態のオクスカルバゼピンを２４時間、水に懸濁した。生成物をＰＸＲＤにより分析し、Ａ形態であると決定した。

実施例１１

B形態からのC形態の調製

B形態のオクスカルバゼピンを外界温度で貯蔵した。得られた物質をＰＸＲＤにより分析し、Ｃ形態であることがわかった。

【００４８】

特別に好ましい実施態様に関して本発明を記載し、それを実施例によって例証したことによって、当業者は、本明細書に開示された本発明の趣旨及び範囲を外れない、記載され、例証された本発明についての変更を理解することができる。

【図面の簡単な説明】

【００４９】

【図１】図１は、Ｂ形態のオクスカルバゼピンのＰＸＲＤパターンである。

【図２】図２は、Ｃ形態のオクスカルバゼピンのＰＸＲＤパターンである。

【図３】図３は、Ｄ形態のオクスカルバゼピンのＰＸＲＤパターンである。

【図４】図４は、Ｅ形態のオクスカルバゼピンのＰＸＲＤパターンである。

【図５】図５は、Ａ形態のオクスカルバゼピンのＰＸＲＤパターンである。

【図１】

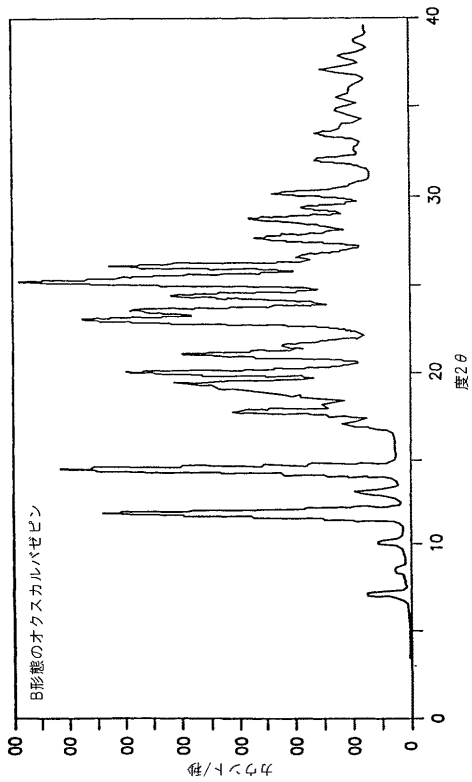


Fig. 1

【図２】

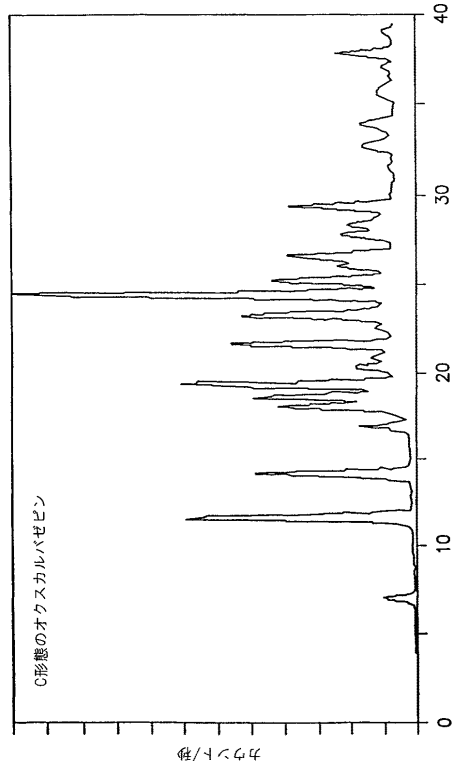


Fig. 2

【図３】

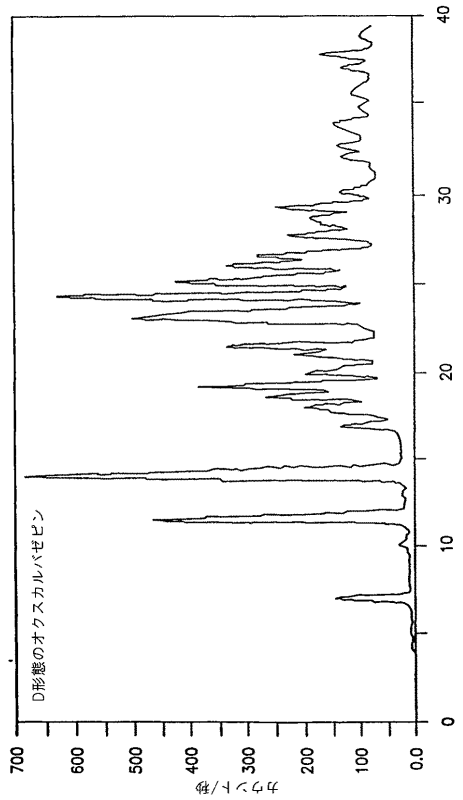


Fig. 3

【図４】

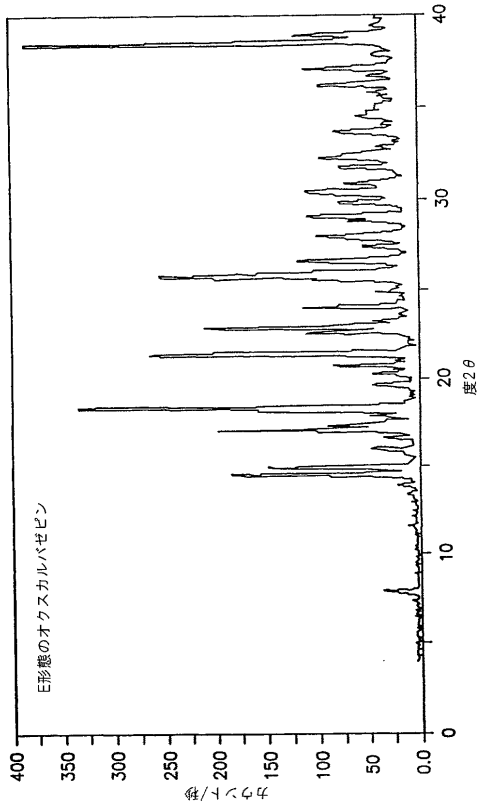


Fig. 4

【図５】

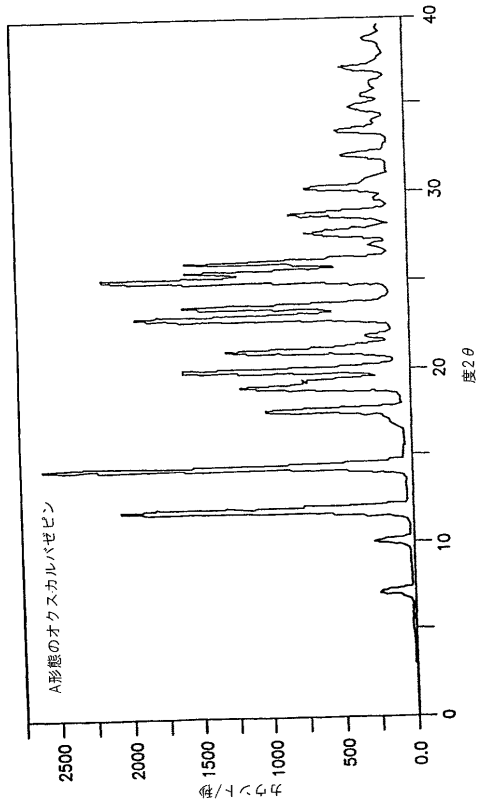


Fig. 5

【国際公開パンフレット】

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(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, Petah Tiqva 49131 (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 91454-1090 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ARONHIME, Judith** [IL/IL]; Rehov Harav Maor Iosef 5a, 76217 Rehovot (IL). **DOLITZKY, Ben-Zion** [IL/IL]; Lohame HaGhetto 32, Petach Tiqva (IL). **BERKOVICH, Yana** [IL/IL]; Ha-Anafa Street 309/20, 93902 Jerusalem (IL). **GARTH, Nissim** [IL/IL]; 9 Derech Achoresh Str., Ramot 97278 (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

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(54) **Title:** NEW CRYSTAL FORMS OF OXCARBAZEPINE AND PROCESSES FOR THEIR PREPARATION

(57) **Abstract:** The present invention provides for new crystal forms of oxcarbazepine, more particularly oxcarbazepine Forms B, C, D and E. The present invention further provides processes for preparation of these forms. Form B is prepared by evaporating the solvents from a solution of oxcarbazepine in toluene and dichloromethane. Form B is also obtained by immediately cooling the solution of oxcarbazepine and toluene. Cooling the same solution at a slower rate, but still fairly rapidly, results in oxcarbazepine Form C. Cooling th same solution at even a slower rate results in another Form, oxcarbazepine Form D. Oxcarbazepine Form E, a solvate of chloroform, is obtained by precipitating a solution of oxcarbazepine and chloroform. The present invention also provides processes for converting one of the newly discovered crystal forms of oxcarbazepine into another crystal form, including Form A, which is in the prior art. These conversions may occur by storage at ambient temperature, by heating one particular form or treatment with a protic solvent.

NEW CRYSTAL FORMS OF OXCARBAZEPINE AND PROCESSES FOR THEIR PREPARATION

CROSS-REFERENCE TO RELATED APPLICATIONS

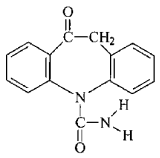
This application claims the benefit under 35 U.S.C. 1.119 (e) of U.S. provisional application No. 60/268,314, filed on February 12, 2001.

FIELD OF THE INVENTION

This invention relates to new crystal forms of oxcarbazepine and processes for their preparation.

BACKGROUND OF THE INVENTION

Oxcarbazepine (10-oxo-10,11-dihydro-5H-dibenz[b, f]azepine-5-carboxamide) of the general formula:



has valuable therapeutic benefits and acts as a central nervous system depressant. Currently it is being marketed as TRILEPTAL®, for treatment of epilepsy. According to the prescribing information for TRILEPTAL®, the pharmacological benefit of oxcarbazepine is primarily exerted through the 10-hydroxy metabolite of oxcarbazepine. In vitro studies indicate that the metabolite blocks voltage sensitive sodium channels, which results in the stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the brain. U.S. Pat. No. 5,658,900, incorporated herein by reference, further teaches the use of oxcarbazepine to treat Parkinson's disease. TRILEPTAL® is administered in a dosage units of 150mg, 300mg and 600mg.

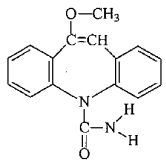
U.S. Patents Nos. 3,716,640; 4,452,738; 4,559,174 and 5,808,058 are hereby incorporated by reference for their disclosures of processes for preparing oxcarbazepine.

The present invention relates to the solid state physical properties of oxcarbazepine prepared by any of the disclosed or other methods. These properties can be influenced by controlling the conditions under which the oxcarbazepine is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular crystalline form of a substance. The crystalline form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by powder X-ray crystallography, solid state ^{13}C NMR spectrometry and infrared spectrometry.

According to U.S. Pat. No. 3,716,640, oxcarbazepine may be prepared from 10-methoxy-5H-dibenz[b, f]azepine-5-carboxamide of formula:



by hydrolysis with hydrochloric acid. Oxcarbazepine with a melting point of 215-216°C was obtained after recrystallization from ethanol.

U.S. Patent No. 4,559,174 contains numerous examples of a process of preparing oxcarbazepine *via* a 5-cyano-10-nitro-5H-dibenz[b,f]acepine intermediate. In these examples, the product was obtained as a precipitate from the mother liquor and in some instances recrystallized and in other instances washed or slurried with solvent to remove impurities. Solvents from which oxcarbazepine was precipitated or recrystallized are chlorobenzene, acetic acid/water, water, isopropanol, acetonitrile and methanol/water.

U.S. Patent No. 5,808,058 teaches that oxcarbazepine may be prepared from N-carbamoylization of 10-methoxyminostilbene with sodium or potassium cyanate in the presence of a strong non-aqueous acid, followed by mild aqueous acid hydrolysis of the methoxy group. In the examples, oxcarbazepine was recrystallized from dimethylacetamide, cyclohexanone, ethylcellosolve, 2:1 DMF:water, methanol and dioxane.

The oxcarbazepine that is formulated into the commercial product TRILEPTAL® is designated herein as oxcarbazepine Form A. Oxcarbazepine Form A is a white to faintly orange crystalline powder. It is slightly soluble in solvents such as chloroform, dichloromethane, acetone and methanol, and practically insoluble in solvents ethanol, ether and water. Due to its low solubility, crystallization of oxcarbazepine from water is impracticable unless the crystallization is carried on from

a hot solution. Crystallization from water and various organic solvents such as acetonitrile, THF, ethyl acetate, EtOH/toluene, dichloromethane, DMA, DMF, cyclohexane, cyclohexanone, alcohols, chloroform, water/DMA, DMA/hexane, DMF/EtOH, DMA, and acetone consistently produce the prior art Form A.

There is a need for discovery of accessible but previously unknown polymorphic forms of a pharmaceutically useful compound because it provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

Four new polymorphic and pseudopolymorphic forms of oxcarbazepine have now been discovered. They can be differentiated by their powder X-ray diffraction ("PXRD") patterns and thermogravimetric analysis ("TGA").

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides oxcarbazepine Form B. According to another aspect, the present invention provides for oxcarbazepine having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta.

According to another aspect, the present invention provides a process for preparing oxcarbazepine Form B comprising the steps of preparing a solution of oxcarbazepine in a mixture of dichloromethane and toluene, and evaporating the toluene and dichloromethane mixture.

According to another aspect, the present invention provides a process for preparing oxcarbazepine Form B comprising the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

According to another aspect, the present invention relates to oxcarbazepine Form C. The present invention relates to oxcarbazepine characterized by PXRD peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form C comprising the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of from about 20 to 60°C min^{-1} to cause formation of a precipitate and separating the precipitate.

In another aspect, the present invention relates to oxcarbazepine Form D. The present invention also relates to oxcarbazepine characterized by PXRD peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form D comprising the steps of preparing a solution of oxcarbazepine in toluene, and evaporating the toluene leaving a residue of oxcarbazepine Form D.

In another aspect, the present invention provides for oxcarbazepine chloroform solvate Form E.

In another aspect, the present invention relates to oxcarbazepine chloroform solvate. The present invention also relates to oxcarbazepine solvate characterized by PXRD peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine solvate Form E comprising causing the formation of a precipitate from a solution of oxcarbazepine in chloroform, and separating the precipitate.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising heating oxcarbazepine solvate Form E.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising heating oxcarbazepine Form B.

In another aspect, the present invention provides a process for the preparation of oxcarbazepine Form C comprising storing oxcarbazepine Form B at ambient temperature.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising contacting the oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C and oxcarbazepine Form D with a protic solvent.

In another aspect, the present invention relates to a pharmaceutical composition comprising oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C, oxcarbazepine Form D and oxcarbazepine Form E, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a PXRD pattern for oxcarbazepine Form B.

Figure 2 is a PXRD pattern for oxcarbazepine Form C.

Figure 3 is a PXRD pattern for oxcarbazepine Form D.

Figure 4 is a PXRD pattern for oxcarbazepine Form E.

Figure 5 is a PXRD pattern of oxcarbazepine Form A.

DETAILED DESCRIPTION OF THE INVENTION

As used herein,the term "solution" refers to a mixture, which preferably is homogeneous. A homogeneous mixture may not result from the initial addition of a solute to a solvent, but only after subsequent heating of the mixture.

It has now been found that new crystal forms, differentiated from prior art Form A, can be obtained by crystallization induced by rapid cooling or evaporation of oxcarbazepine solutions in toluene, toluene:dichloromethane mixtures and chloroform.

Four novel crystal forms of oxcarbazepine have been isolated and characterized. These forms are distinguished by their PXRD patterns. The DSC profile of all the samples shows a melting peak concomitant to decomposition at about 230 °C.

Generally, in PXRD, compounds can be characterized by the position and intensity of diffraction peaks. However, the intensity of the peaks can differ from sample to sample, due to, among other things, orientation effects. In some crystal habits certain orientations are preferred which enhance some diffraction peaks and reduce others. We describe below as "major" or "strongest" peaks the largest peaks in the samples we measured. However, these peaks may not be the largest peaks in

some samples or preparations due to the orientation effects. The peak positions, on the other hand, are largely unaffected by orientation effects.

The present invention provides a novel form of oxcarbazepine designated Form B. The oxcarbazepine Form B may be characterized by a PXRD pattern (Fig. 1) with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta. More particularly, the oxcarbazepine Form B may be characterized by a PXRD pattern with peaks at about 11.9, 14.4, 17.7, 19.4, 20.0, 21.1, 23.0, 24.0, 24.4 ,25.1, 26.0 ± 0.2 degrees two-theta.

Form B may be obtained by preparing a solution of oxcarbazepine in dichloromethane, adding the solution to toluene and evaporating the mixed solvent at a controlled rate. Oxcarbazepine is preferably dissolved in dichloromethane in a weight ratio of from about 1: 66 to about 1:116, more preferably about 1:110. After dissolution of the oxcarbazepine, toluene is added, preferably in an amount of from about 9.4 ml g^{-1} dichloromethane to about 12.8 ml g^{-1} dichloromethane, more preferably about 8.5 ml g^{-1}. Oxcarbazepine crystallizes during evaporation of the solvent mixture into Form B when the solvent is evaporated at from about 1/30 to about 1/50 of its initial volume per minute, more preferably about 1/40 its initial volume per minute. This rate of evaporation can be obtained using a conventional rotary evaporator with aspirator vaccum, without warming the flask. Preferably, oxcarbarzepine is added to the dichloromethane in such a manner that a homogeneous mixture is obtained.

Form B may be prepared by an alternative process that comprises the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

Oxcarbazepine is first added to toluene to form a solution, preferably in a ratio of from about 8 mg to about 10 mg oxcarbazepine per gram of toluene. The solution is then heated, preferably to reflux for a sufficient time to substantially dissolve the oxcarbazepine in toluene.

The solution is then cooled very rapidly to about 0°C, *i.e.* at a rate of about 60°C min^{-1} or faster. Such rapid cooling may be acheived by dipping the sample in salt ice bath at a temperature of -13°C. Rapidly cooling the solution leads to the formation of the apparently kinetically favored product oxcarbazepine Form B.

Oxcarbazepine precipitates from the solution in less than about five minutes, and is then separated. Preferably, a filter is used to separate the oxcarbazepine Form B. To filter, the solution may be passed through paper, glass fiber or other membrane material or a clarifying agent such as celite.

The present invention also provides oxcarbazepine Form C. Oxcarbazepine Form C is characterized by a PXRD pattern (Fig. 2) with peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta. More particularly, Form C is characterized by peaks at about 11.7, 17.0, 18.0, 21.7, 23.2, 24.4, 26.0 ± 0.2 degrees two-theta.

The present invention also provides a process for preparing oxcarbazepine Form C comprising the steps of preparing a solution of oxcarbazepine and toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

Oxcarbazepine is added to toluene to form a solution which is subsequently heated. Preferably, oxcarbazepine is added in an amount of from about 7.3 mg ml^{-1} to about 9.0 mg ml^{-1}, more preferably about 8.1 mg ml^{-1}. The solution is preferably heated to from about 25°C to about reflux, with temperatures at or near reflux being most preferred. One skilled in the art may appreciate that the solution may be completely homogeneous only after the heating step.

After heating for about 10 minutes, the solution is then cooled rapidly. The solution is cooled at a slower rate than is used to obtain Form B, but rapidly enough to allow for the formation of oxcarbazepine Form C as major product. Preferably, the solution is cooled at a rate of about 20°C to about 60°C per minute, and most preferably at a rate of about 40°C per minute. To cool the solution at a rate of 40C per minute, an ice water bath with a temperature of 0°C may be used,

The solution is preferably cooled to about 0°C. One skilled in the art may appreciate that other temperatures may also suffice as long as they allow for the substantial formation of Form C. After cooling, a precipitate forms, which is then separated. Preferably, the precipitate is separated with a filter. To filter, the solution may be passed through paper, glass fiber or other membrane materials, or a clarifying agent such as celite.

The present invention also provides oxcarbazepine Form D. Oxcarbazepine Form D is characterized by a PXRD pattern (Fig. 3) with peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

The present invention provides a process for preparing oxcarbazepine Form D comprising the steps of preparing a solution of oxcarbazepine in toluene, and evaporating the toluene from the solution.

Oxcarbazepine is first added to toluene to form a solution. Oxcarbazepine is preferably added in an amount of from about 8.5 to about 9.5 milligrams per gram of toluene, more preferably about 9.1 mg g^{-1}.

The solution is then preferably heated to completely dissolve the oxcarbazepine. The solution is preferably refluxed for a short amount of time, about five minutes, though a different of temperature and amount of time may also achieve the same result. One skilled in the art may appreciate that the solution may become completely homogeneous only after the heating step.

After heating, the solution is then preferably cooled to decrease the solubility of oxcarbazepine in the toluene. The solution is cooled at a slower rate than the processes resulting in Forms B and C. The solution is cooled at a rate of 20°C min^{-1} and below, more preferably at a rate of about 10°C min^{-1} to about 20°C min^{-1}, and most preferably at a rate of 15°C min^{-1}. The solution is cooled in such a way that a precipitate does not substantially form during cooling.

The solution is preferably cooled to from about 0°C to about room temperature, most preferably to about 0°C. One skilled in the art may appreciate that other temperatures may achieve the same result.

After cooling, the toluene is removed by evaporation. The toluene may be evaporated under ambient or reduced pressure, or optionally heated to accelerate the evaporation. After evaporation, a residue remains which PXRD analysis has confirmed is oxcarbazepine Form D.

The process for the preparation of Form B in Example 1 and the process for the preparation of Form D are similar. To prepare Form D, oxcarbazepine is first added to toluene and then the toluene is evaporated. To prepare Form B, oxcarbazepine is first dissolved in dichloromethane and is added to toluene as a solution. The mixed solvent is then removed by evaporation to obtain Form B.

The present invention also provides oxcarbazepine as a solvate of chloroform. The oxcarbazepine solvate of the present invention is characterized by a PXRD pattern (Fig. 4) with peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta. More particularly, the present invention provides for oxcarbazepine chloroform solvate Form E.

This form contains about 27% solvent, which corresponds to a ¾ solvate of chloroform. The solvent content was measured by TGA, and a weight loss of 27% was seen between 30°C and 90°C. This desolvatation is also observed in the DSC as an endotherm in the temperature range of about 40°C to 90°C.

The present invention also provides a process for preparing oxcarbazepine solvate Form E comprising causing formation of a precipitate from a solution of oxcarbazepine and chloroform, and separating the precipitate. The conditions used are different than that of producing Form A by crystallization from chloroform, for instance dissolution at reflux and cooling at 10°C min^{-1} rate.

Oxcarbazepine is first dissolved in chloroform to form a solution. Oxcarbazepine is preferably added in an amount of from about 6.8 to about 8.0 milligrams per gram of chloroform, more preferably about 7.3 mg g^{-1}. The solution is then preferably heated to increase the amount of oxcarbazepine taken up by the chloroform. Preferably, the solution is completely homogeneous after the heating step. The solution is preferably heated from about 50°C to about 60°C, and most preferably to about 55°C.

After heating, the solution is cooled. Preferably, the solution is cooled to a temperature at or below room temperature. Most preferably, the solution is cooled to about 16°C. The solubility of chloroform for oxcarbazepine decreases as the solution is cooled. To allow the solution to be cooled to a low temperature of about 16°C without premature precipitation, the solution may first be cooled to a first temperature, and after a while to a second, lower temperature. Preferably, the solution is first cooled to about 25°C, and then to below room temperature. After cooling, a precipitate forms. The precipitate may be separated using a filter. Before filtering, the solution may be allowed to warm. Preferably, the solution is warmed to about 25°C.

The present invention also provides for processes that convert one form of oxcarbazepine into another form of oxcarbazepine. Form A may be obtained by heating oxcarbazepine solvate Form E at elevated temperatures between 40°C and 80°C, preferably 60°C, for a period of 2 hours to 10 hours, preferably 4 hours. One skilled in the art may appreciate that Form E may transform to Form A under different conditions, and that the optimal conditions may be discovered with routine experimentation.

The present invention also provides a process for transforming Form B to Form C. It was found that Form B transforms to Form C at from about 20 to about 30°C, *i.e.* at about room temperature. The transformation is gradual and prolonged, and may occur over several months. One skilled in the art may appreciate that the optimal conditions and time for transformation may be discovered through routine experimentation.

The present invention also provides a process for transforming Form B to Form A. At about ambient temperature, Form B transforms to Form C. One skilled in the art would appreciate that such a transition may also occur at temperatures above and below ambient temperature, and that by routine experimentation the boundary of the temperature range may be determined. At higher temperatures, between 60°C and 120°C, preferably 60°C, a transformation from form B to form A occurs after a few hours, as determined by the temperature. The temperature at which Form B transforms to Form A rather than Form C may be determined by routine experimentation. One skilled in the art may appreciate that the rate and extent of the transformation varies with the conditions and the amount of time under which the transformation occurs.

The present invention also provides a process for transforming Forms B, C, and D to Form A. It was found that Forms B, C or D may transform readily to the prior art Form A by slurry in protic solvents like ethanol or water for a period between several hours and several days, preferably for a period of 24 hours. One skilled in the art may appreciate that other protic solvents may be used and the optimal conditions may be determined through routine experimentation.

The pharmaceutical compositions of the present invention have valuable therapeutic benefits and act as a central nervous system depressant. The pharmaceutical compositions of the present invention may be used to treat epilepsy by preventing or reducing the extent of seizures. The pharmacological benefit of the compositions is primarily exerted through the 10-monohydroxy metabolite of oxcarbazepine. In vitro studies indicate that the metabolite blocks voltage sensitive sodium channels, which results in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and dimunition of propagation of synaptic impulses. The phamaceutical compositions of the present invention may also be used to treat Parkinson's disease.

Pharmaceutical compositions of the present invention contain oxcarbazepine Form B, C, D and/or E, optionally in mixture with other Form(s), or amorphous oxcarbazepine and/or active ingredients. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition 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 care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelitinized 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®), 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®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution 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®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) 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 dixoide, 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 sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor 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, clopidogrel hydrogensulfate and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

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, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, 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, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin 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 hydroxy toluene, 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 guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, 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.

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 losenges, 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 gelatin and optionally contain a plasticizer such as glycerin 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 tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be 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 tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

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

The solid unit dosage forms of the present invention preferably contain about 150, 300 or 600 mg of oxcarbazepine. The unit dosage form as used herein refers to the amount of the various forms of oxcarbazepine contained in the vehicle of administration, such as a tablet or a capsule. Most preferably, the unit dosage form of the present invention is administered as a tablet.

The tablet of the present invention is preferably film-coated and contains the following inactive ingredients: colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc and titanium dioxide; yellow iron oxide.

The liquid unit dosage forms of the present invention contain about 300 mg of oxcarbazepine in a suspension with 5mL of liquid. Most preferably, the suspension is administered orally and has about 60mg of oxcarbazepine for every milliliter of liquid.

The oral suspension of the present invention preferably contains the following inactive ingredients: ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

The characterization of crystalline phases were performed using Phillips PW 1710 Diffractometer. Thermograviometric analysis (TGA) was produced using Mettler TG50 equipped with Mettler TC11 TA processor. Differential Scanning calorimetry (DSC) was performed using Mettler DSC 30 apparatus. FTIR spectra were recorded using Nicolet Avatar 360 spectrometer.

One skilled in the art may appreciate that other unit dosages may be made as necessary in a routine fashion.

EXAMPLES

Example 1

Preparation of Form B

Oxcarbazepine (0.15 g) was dissolved in dichloromethane (20 g) at room temperature. After complete dissolution, the solution was added to toluene (170 mL). After stirring for 5 minutes the solvent was evaporated at the rate of 5 g $min.^{-1}$ until dryness. The resulting material was analyzed by PXRD and found to be form B.

Example 2

Preparation of Form B

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 5 minutes the reaction mixture was cooled immediately to 0°C. After 5 minutes, the suspension was filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be Form B.

Example 3

Preparation of Form C

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 10 minutes the reaction mixture was cooled to 0°C at the rate of 40°C per minute. After 5 minutes, the suspension was filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be Form C.

Example 4

Preparation of Form D

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 5 minutes the reaction mixture was cooled to 0°C. After 5 minutes, the solvent was evaporated. The resulting material was analyzed by PXRD and found to be Form D.

Example 5

Preparation of solvated Form E

Oxcarbazepine (1.1 g) was dissolved in chloroform (150 g) at room temperature. After heating to about 55°C for 5 minutes the reaction mixture was cooled to 21.5°C, and after 8 hours the reaction mixture was cooled to 16°C. After 48 hours the suspension was heated to 25°C, and filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be solvated form E.

Example 6

Preparation of Form A from Form E

Oxcarbazepine solvate Form E was heated to a temperature of 60°C and maintained at that temperature for 4 hours. The resulting material was analyzed by PXRD, which showed oxcarbazepine Form A .

Example 7

Preparation of Form A from Form B

Oxcarbazepine Form B was heated to a temperature of about 60°C and was maintained at that temperature for five hours. The resulting material was analyzed by PXRD, which showed oxcarbazepine Form A.

Example 8

Preparation of Form A from Form B

Oxcarbazepine Form B was suspended in ethanol for 24 hours. The product was analyzed by PXRD and determined to be Form A.

Example 9

Preparation of Form A from Form C

Oxcarbazepine Form C was suspended in ethanol for 24 hours. The product was analyzed by PXRD and determined to be Form A.

Example 10

Preparation of Form A from Form D

Oxcarbazepine Form D was suspended in water for 24 hours. The product is analyzed by PXRD and is determined to be Form A.

Example 11

Preparation of Form C from Form B

Oxcarbazepine Form B was stored at an ambient temperature. The resulting material was analyzed by PXRD and found to be Form C.

Having described the invention with reference to particular preferred embodiments and illustrated it with examples, those in the art may appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification.

CLAIMS

What is claimed is:

1. Oxcarbazepine Form B.

2. Oxcarbazepine having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta.

3. The oxcarbazepine of claim **2** having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 17.7, 19.4, 20.0, 21.1, 23.0, 24.0, 24.4 ,25.1, 26.0 ± 0.2 degrees two-theta.

4. The oxcarbazepine of claim **3** having a PXRD diffraction pattern substantially as depicted in figure 1.

5. A process for preparing oxcarbazepine Form B comprising the steps of:
   a) preparing a solution of oxcarbazepine in a mixture of dichloromethane and toluene, and
   b) evaporating the toluene and the dichloromethane leaving Form B as a residue.

6. The process of claim **5**, wherein the solution is prepared by dissolving oxcarbazepine in dichloromethane and adding the dichloromethane to toluene.

7. The oxcarbazepine Form B prepared by the process of claim **5**.

8. A process for preparing oxcarbazepine Form B comprising the steps of:
   a) preparing a solution of oxcarbazepine in toluene;
   b) heating the solution;

c) cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate; and

d) separating the precipitate.

9. The process of claim **8**, wherein the solution is heated to about reflux.

10. The process of claim **8**, wherein the solution is cooled to a temperature of about 0°C.

11. The oxcarbazepine Form B prepared by the process of claim **8**.

12. Oxcarbazepine Form C.

13. Oxcarbazepine characterized by PXRD peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta

14. The oxcarbazepine of claim **13** characterized by PXRD peaks at about 11.7, 17.0, 18.0, 21.7, 23.2, 24.4, 26.0 ± 0.2 degrees two-theta.

15. The oxcarbazepine of claim **14** characterized by a PXRD diffraction pattern substantially as depicted in figure 2.

16. A process for preparing oxcarbazepine Form C comprising the steps of:

a) preparing a solution of oxcarbazepine in toluene;

b) heating the solution;

c) cooling the solution at a rate of from about 20 to 60°C $min.^{-1}$ to cause formation of a precipitate; and

d) separating the precipitate.

17. The process of claim **16**, wherein the solution is cooled at a rate of about 40°C

per minute.

18. The process of claim **16**, wherein the solution is cooled to about 0°C.

19. The process of claim **16**, wherein the solution is heated to about reflux.

20. The oxcarbazepine Form C prepared by the process of claim **16**.

21. Oxcarbazepine Form D.

22. Oxcarbazepine characterized by PXRD peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

23. The oxcarbazepine of claim **22** characterized by a PXRD diffraction pattern substantially as depicted in figure 3.

24. A process for preparing oxcarbazepine Form D comprising the steps of:
    a) preparing a solution of oxcarbazepine in toluene; and
    b) evaporating the toluene leaving a residue of oxcarbazepine Form D.

25. The process of claim **24**, further comprising a step of heating the solution before evaporating.

26. The process of claim **25**, wherein the solution is heated to about reflux.

27. The process of claim **25**, further comprising cooling the heated solution before evaporating.

28. The process of claim **27**, wherein the solution is cooled to about 0°C.

29. The process of claim **24**, further comprising a step of cooling the solution.

30. The process of claim **29**, wherein the solution is cooled to about 0°C.

31. The process of claim **24**, wherein the toluene is removed from the solution by evaporation.

32. The oxcarbazepine Form D prepared by the process of claim **24**.

33. An oxcarbazepine chloroform solvate.

34. Oxcarbazepine chloroform solvate Form E.

35. An oxcarbazepine chloroform solvate characterized by a PXRD pattern with peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta.

36. The oxcarbazepine solvate of claim **35** characterized by a PXRD diffraction pattern substantially as depicted in figure 4.

37. The oxcarbazepine chloroform solvate of claim **33** containing about a 27 weight % chloroform.

38. A process for preparing oxcarbazepine chloroform solvate comprising:
    a) causing formation of a precipitate from a solution of oxcarbazepine in chloroform, and
    b) separating the precipitate.

39. The process of claim **38**, further comprising a step of heating the solution before causing formation of the precipitate.

40. The process of claim **39**, further comprising a step of cooling the heated solution, whereby cooling causes formation of the precipitate.

41. The process of claim **39**, wherein the solution is heated to an elevated temperature of from about 50°C to about 60°C.

42. The process of claim **41**, wherein the solution is heated to an elevated temperature of about 55°C.

43. The process of claim **41**, wherein the heated solution is cooled to a reduced temperature of from about 10°C to about 20°C.

44. The process of claim **43**, wherein the reduced temperature is about 16°C.

45. The oxcarbazepine chloroform solvate produced by the process of claim **37**.

46. A process for preparing oxcarbazepine Form A comprising:
    a) providing oxcarbazepine chloroform solvate Form E,
    b) heating the oxcarbazepine chloroform solvate, and
    c) recovering oxcarbazepine as Form A.

47. The process of claim **46**, wherein the oxcarbazepine solvate Form E is heated to an elevated temperature in the range of from about 40°C to about 80°C.

48. The process of claim **47**, wherein the elevated temperature is about 60°C.

49. A process for preparing oxcarbazepine Form A comprising
    a) providing oxcarbazepine Form B,
    b) heating the oxcarbazepine, and

c) recovering the oxcarbazepine as Form A.

50. The process of claim **49**, wherein oxcarbazepine Form B is heated to an elevated temperature in the range of from about 60°C to about 120°C.

51. The process of claim **50**, wherein the elevated temperature is about 60°C.

52. A process for the preparation of oxcarbazepine Form C comprising
a) providing oxcarbazepine Form B,
b) maintaining the oxcarbazepine at a temperature in the range of from about 20 to about 30°C, and
c) recovering the oxcarbazepine as Form C.

53. A process for preparing oxcarbazepine Form A comprising:
a) contacting oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C and oxcarbazepine Form D with a protic solvent; and
b) recovering oxcarbazepine as Form A.

54. The process of claim **53**, wherein the forms of oxcarbazepine are suspended in the protic solvent.

55. The process of claim **53**, wherein the protic solvent is selected from the group consisting of water and ethanol.

56. The process of claim **54**, wherein the oxcarbazepine is suspended in the protic solvent from about two hours to about three days.

57. The process of claim **56**, wherein the oxcarbazepine is suspended for about one day.

58. A pharmaceutical composition comprising:
    a) oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C, oxcarbazepine Form D and oxcarbazepine Form E; and
    b) a pharmaceutically acceptable excipient.

59. The pharmaceutical composition of claim **58**, wherein the composition is mixed with one or more forms of oxcarbazepine.

60. A pharmaceutical dosage form comprising the pharmaceutical composition of claim **58**.

61. The pharmaceutical dosage form of claim **60**, wherein the dosage form is a capsule or tablet.

62. The pharmaceutical dosage form of claim **61**, wherein the dosage form is a tablet.

63. The pharmaceutical dosage form of claim **60**, containing a unit dosage of about 150mg to about 600mg oxcarbazepine.

64. The pharmaceutical dosage form of claim **63**, containing a unit dosage selected from the group consisting of about 150mg, 300mg and 600mg.

65. The pharmaceutical dosage form of claim **60**, wherein the dosage form is an oral suspension.

66. The pharmaceutical dosage form of claim **65**, wherein the dosage is about 60mg ml^{-1}.

67. The pharmaceutical dosage form of claim **66**, wherein the dosage is about 300mg ml^{-1}.

68. A method of preventing or reducing the severity of seizures comprising administrating the pharmaceutical composition of claim **58**.

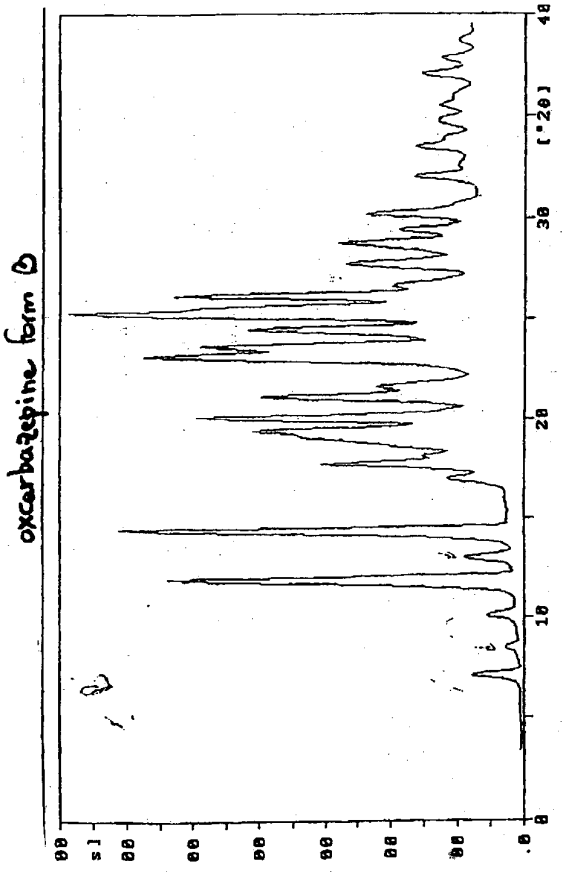
69. The method of claim **68**, wherein the seizures are associated with epilepsy.

70. A method of treating Parkinson's disease comprising administrating the pharmaceutical composition of claim **58**.

71. A method of depressing the central nervous system comprising administering the pharmaceutical composition of claim **58**.

72. The method of claim **71**, wherein the central nervous system is depressed by blocking voltage sensitive sodium channels.

figure 1



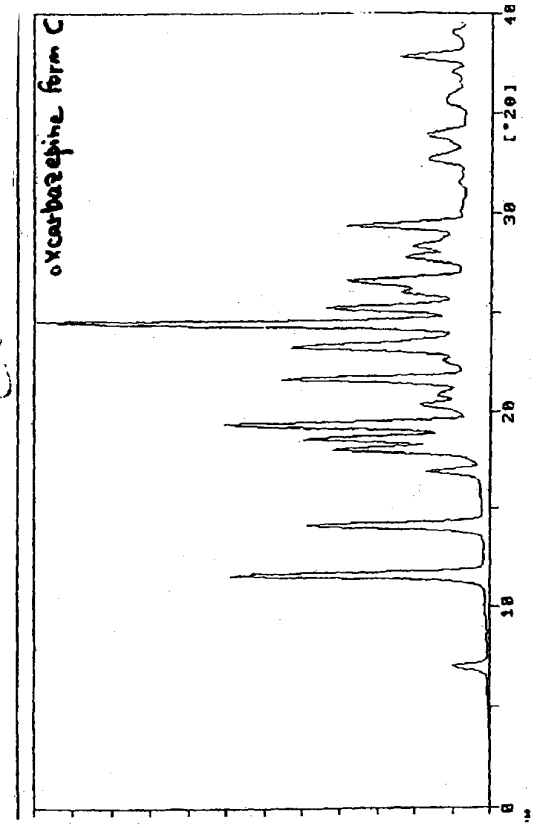


Figure 2C

figure 3

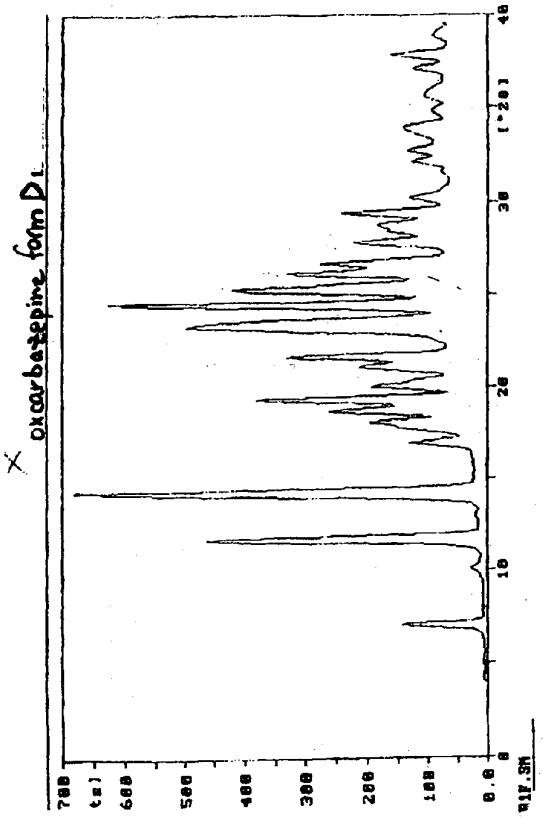
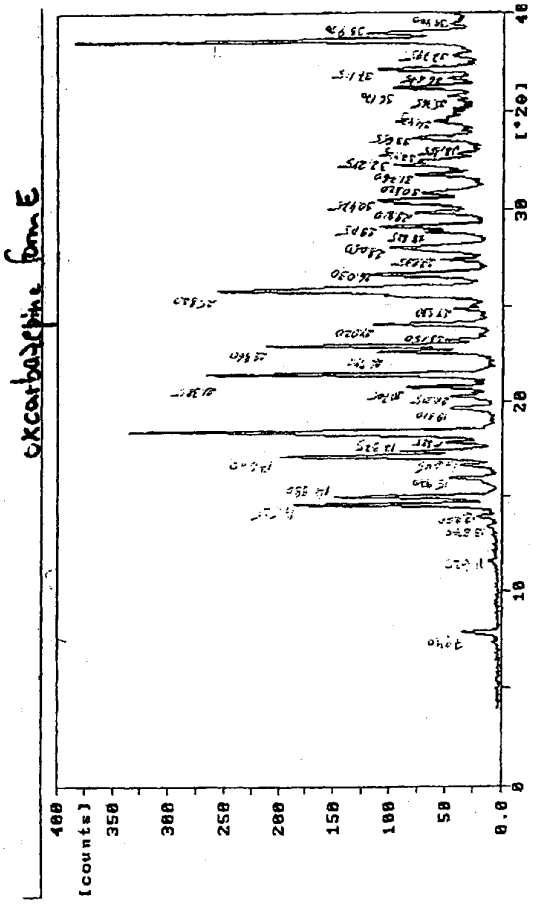

oxcarbazepine form B
700
600
500
400
300
200
100
0.0
10
20
30
40
[°2θ]

Figure 4


oxcarbazepine form E
[counts]
[°2θ]
0.0
10
20
30
40
50
100
150
200
250
300
350
400

OXCARBAZEPINE FORM A

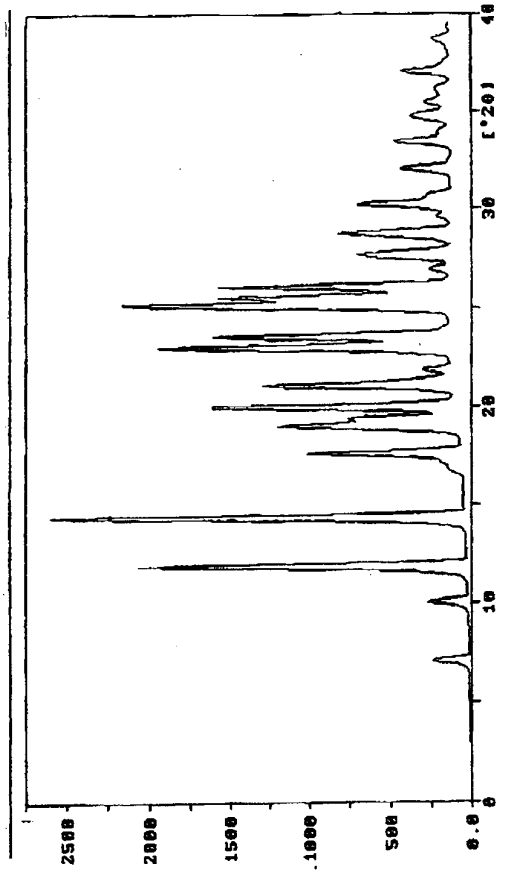


figure 5

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(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, Petah Tiqva 49131 (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 91454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARONHIME, Judith** [IL/IL]; Rehov Harav Maor Iosef 5a, 76217 Rehovot (IL). **DOLITZKY, Ben-Zion** [IL/IL]; Lohame HaGhette 32, Petach Tiqva (IL). **BERKOVICH, Yana** [IL/IL]; Ha-Anafa Street 309/20, 93902 Jerusalem (IL). **GARTH, Nissim** [IL/IL]; 9 Derech Achoresh Str., Ramot 97278 (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

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(57) Abstract: The present invention provides for new crystal forms of oxcarbazepine, more particularly oxcarbazepine Forms B, C, D and E. The present invention further provides processes for preparation of these forms. Form B is prepared by evaporating the solvents from a solution of oxcarbazepine in toluene and dichloromethane. Form B is also obtained by immediately cooling the solution of oxcarbazepine and toluene. Cooling the same solution at a slower rate, but still fairly rapidly, results in oxcarbazepine Form C. Cooling th same solution at even a slower rate results in another Form, oxcarbazepine Form D. Oxcarbazepine Form E, a solvate of chloroform, is obtained by precipitating a solution of oxcarbazepine and chloroform. The present invention also provides processes for converting one of the newly discovered crystal forms of oxcarbazepine into another crystal form, including Form A, which is in the prior art. These conversions may occur by storage at ambient temperature, by heating one particular Form or treatment with a protic solvent.

【国際公開パンフレット（コレクトバージョン）】

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(57) Abstract: The present invention provides for new crystal forms of oxcarbazepine, more particularly oxcarbazepine Forms B, C, D and E. The present invention further provides processes for preparation of these forms. Form B is prepared by evaporating the solvents from a solution of oxcarbazepine in toluene and dichloromethane. Form B is also obtained by immediately cooling the solution of oxcarbazepine and toluene. Cooling the same solution at a slower rate, but still fairly rapidly, results in oxcarbazepine Form C. Cooling th same solution at even a slower rate results in another Form, oxcarbazepine Form D. Oxcarbazepine Form E, a solvate of chloroform, is obtained by precipitating a solution of oxcarbazepine and chloroform. The present invention also provides processes for converting one of the newly discovered crystal forms of oxcarbazepine into another crystal form, including Form A, which is in the prior art. These conversions may occur by storage at ambient temperature, by heating one particular Form or treatment with a protic solvent.

NEW CRYSTAL FORMS OF OXCARBAZEPINE AND PROCESSES FOR THEIR PREPARATION

CROSS-REFERENCE TO RELATED APPLICATIONS

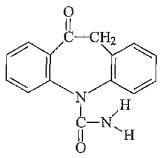
This application claims the benefit under 35 U.S.C. 1.119 (e) of U.S. provisional application No. 60/268,314, filed on February 12, 2001.

FIELD OF THE INVENTION

This invention relates to new crystal forms of oxcarbazepine and processes for their preparation.

BACKGROUND OF THE INVENTION

Oxcarbazepine (10-oxo-10,11-dihydro-5H-dibenz[b, f]azepine-5-carboxamide) of the general formula:



has valuable therapeutic benefits and acts as a central nervous system depressant. Currently it is being marketed as TRILEPTAL®, for treatment of epilepsy. According to the prescribing information for TRILEPTAL®, the pharmacological benefit of oxcarbazepine is primarily exerted through the 10-hydroxy metabolite of oxcarbazepine. In vitro studies indicate that the metabolite blocks voltage sensitive sodium channels, which results in the stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the brain. U.S. Pat. No. 5,658,900, incorporated herein by reference, further teaches the use of oxcarbazepine to treat Parkinson's disease. TRILEPTAL® is administered in a dosage units of 150mg, 300mg and 600mg.

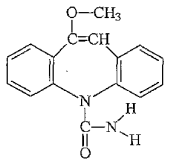
U.S. Patents Nos. 3,716,640; 4,452,738; 4,559,174 and 5,808,058 are hereby incorporated by reference for their disclosures of processes for preparing oxcarbazepine.

The present invention relates to the solid state physical properties of oxcarbazepine prepared by any of the disclosed or other methods. These properties can be influenced by controlling the conditions under which the oxcarbazepine is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular crystalline form of a substance. The crystalline form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by powder X-ray crystallography, solid state ^{13}C NMR spectrometry and infrared spectrometry.

According to U.S. Pat. No. 3,716,640, oxcarbazepine may be prepared from 10-methoxy-5H-dibenz[b, f]azepine-5-carboxamide of formula:



by hydrolysis with hydrochloric acid. Oxcarbazepine with a melting point of 215-216°C was obtained after recrystallization from ethanol.

U.S. Patent No. 4,559,174 contains numerous examples of a process of preparing oxcarbazepine *via* a 5-cyano-10-nitro-5H-dibenz[b,f]acepine intermediate. In these examples, the product was obtained as a precipitate from the mother liquor and in some instances recrystallized and in other instances washed or slurried with solvent to remove impurities. Solvents from which oxcarbazepine was precipitated or recrystallized are chlorobenzene, acetic acid/water, water, isopropanol, acetonitrile and methanol/water.

U.S. Patent No. 5,808,058 teaches that oxcarbazepine may be prepared from N-carbamoylization of 10-methoxyminostilbene with sodium or potassium cyanate in the presence of a strong non-aqueous acid, followed by mild aqueous acid hydrolysis of the methoxy group. In the examples, oxcarbazepine was recrystallized from dimethylacetamide, cyclohexanone, ethylcellosolve, 2:1 DMF:water, methanol and dioxane.

The oxcarbazepine that is formulated into the commercial product TRILEPTAL® is designated herein as oxcarbazepine Form A. Oxcarbazepine Form A is a white to faintly orange crystalline powder. It is slightly soluble in solvents such as chloroform, dichloromethane, acetone and methanol, and practically insoluble in solvents ethanol, ether and water. Due to its low solubility, crystallization of oxcarbazepine from water is impracticable unless the crystallization is carried on from

a hot solution. Crystallization from water and various organic solvents such as acetonitrile, THF, ethyl acetate, EtOH/toluene, dichloromethane, DMA, DMF, cyclohexane, cyclohexanone, alcohols, chloroform, water/DMA, DMA/hexane, DMF/EtOH, DMA, and acetone consistently produce the prior art Form A.

There is a need for discovery of accessible but previously unknown polymorphic forms of a pharmaceutically useful compound because it provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

Four new polymorphic and pseudopolymorphic forms of oxcarbazepine have now been discovered. They can be differentiated by their powder X-ray diffraction ("PXRD") patterns and thermogravimetric analysis ("TGA").

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides oxcarbazepine Form B. According to another aspect, the present invention provides for oxcarbazepine having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta.

According to another aspect, the present invention provides a process for preparing oxcarbazepine Form B comprising the steps of preparing a solution of oxcarbazepine in a mixture of dichloromethane and toluene, and evaporating the toluene and dichloromethane mixture.

According to another aspect, the present invention provides a process for preparing oxcarbazepine Form B comprising the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

According to another aspect, the present invention relates to oxcarbazepine Form C. The present invention relates to oxcarbazepine characterized by PXRD peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form C comprising the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of from about 20 to 60°C min-1 to cause formation of a precipitate and separating the precipitate.

In another aspect, the present invention relates to oxcarbazepine Form D. The present invention also relates to oxcarbazepine characterized by PXRD peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form D comprising the steps of preparing a solution of oxcarbazepine in toluene, and evaporating the toluene leaving a residue of oxcarbazepine Form D.

In another aspect, the present invention provides for oxcarbazepine chloroform solvate Form E.

In another aspect, the present invention relates to oxcarbazepine chloroform solvate. The present invention also relates to oxcarbazepine solvate characterized by PXRD peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta.

In another aspect, the present invention provides a process for preparing oxcarbazepine solvate Form E comprising causing the formation of a precipitate from a solution of oxcarbazepine in chloroform, and separating the precipitate.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising heating oxcarbazepine solvate Form E.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising heating oxcarbazepine Form B.

In another aspect, the present invention provides a process for the preparation of oxcarbazepine Form C comprising storing oxcarbazepine Form B at ambient temperature.

In another aspect, the present invention provides a process for preparing oxcarbazepine Form A comprising contacting the oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C and oxcarbazepine Form D with a protic solvent.

In another aspect, the present invention relates to a pharmaceutical composition comprising oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C, oxcarbazepine Form D and oxcarbazepine Form E, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a PXRD pattern for oxcarbazepine Form B.

Figure 2 is a PXRD pattern for oxcarbazepine Form C.

Figure 3 is a PXRD pattern for oxcarbazepine Form D.

Figure 4 is a PXRD pattern for oxcarbazepine Form E.

Figure 5 is a PXRD pattern of oxcarbazepine Form A.

DETAILED DESCRIPTION OF THE INVENTION

As used herein,the term "solution" refers to a mixture, which preferably is homogeneous. A homogeneous mixture may not result from the initial addition of a solute to a solvent, but only after subsequent heating of the mixture.

It has now been found that new crystal forms, differentiated from prior art Form A, can be obtained by crystallization induced by rapid cooling or evaporation of oxcarbazepine solutions in toluene, toluene:dichloromethane mixtures and chloroform.

Four novel crystal forms of oxcarbazepine have been isolated and characterized. These forms are distinguished by their PXRD patterns. The DSC profile of all the samples shows a melting peak concomitant to decomposition at about 230 °C.

Generally, in PXRD, compounds can be characterized by the position and intensity of diffraction peaks. However, the intensity of the peaks can differ from sample to sample, due to, among other things, orientation effects. In some crystal habits certain orientations are preferred which enhance some diffraction peaks and reduce others. We describe below as "major" or "strongest" peaks the largest peaks in the samples we measured. However, these peaks may not be the largest peaks in

some samples or preparations due to the orientation effects. The peak positions, on the other hand, are largely unaffected by orientation effects.

The present invention provides a novel form of oxcarbazepine designated Form B. The oxcarbazepine Form B may be characterized by a PXRD pattern (Fig. 1) with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta. More particularly, the oxcarbazepine Form B may be characterized by a PXRD pattern with peaks at about 11.9, 14.4, 17.7, 19.4, 20.0, 21.1, 23.0, 24.0, 24.4 ,25.1, 26.0 ± 0.2 degrees two-theta.

Form B may be obtained by preparing a solution of oxcarbazepine in dichloromethane, adding the solution to toluene and evaporating the mixed solvent at a controlled rate. Oxcarbazepine is preferably dissolved in dichloromethane in a weight ratio of from about 1: 66 to about 1:116, more preferably about 1:110. After dissolution of the oxcarbazepine, toluene is added, preferably in an amount of from about 9.4 ml g^{-1} dichloromethane to about 12.8 ml g^{-1} dichloromethane, more preferably about 8.5 ml g^{-1}. Oxcarbazepine crystallizes during evaporation of the solvent mixture into Form B when the solvent is evaporated at from about 1/30 to about 1/50 of its initial volume per minute, more preferably about 1/40 its initial volume per minute. This rate of evaporation can be obtained using a conventional rotary evaporator with aspirator vaccum, without warming the flask. Preferably, oxcarbarzepine is added to the dichloromethane in such a manner that a homogeneous mixture is obtained.

Form B may be prepared by an alternative process that comprises the steps of preparing a solution of oxcarbazepine in toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

Oxcarbazepine is first added to toluene to form a solution, preferably in a ratio of from about 8 mg to about 10 mg oxcarbazepine per gram of toluene. The solution is then heated, preferably to reflux for a sufficient time to substantially dissolve the oxcarbazepine in toluene.

The solution is then cooled very rapidly to about 0°C, *i.e.* at a rate of about 60°C min^{-1} or faster. Such rapid cooling may be acheived by dipping the sample in salt ice bath at a temperature of -13°C. Rapidly cooling the solution leads to the formation of the apparently kinetically favored product oxcarbazepine Form B.

Oxcarbazepine precipitates from the solution in less than about five minutes, and is then separated. Preferably, a filter is used to separate the oxcarbazepine Form B. To filter, the solution may be passed through paper, glass fiber or other membrane material or a clarifying agent such as celite.

The present invention also provides oxcarbazepine Form C. Oxcarbazepine Form C is characterized by a PXRD pattern (Fig. 2) with peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta. More particularly, Form C is characterized by peaks at about 11.7, 17.0, 18.0, 21.7, 23.2, 24.4, 26.0 ± 0.2 degrees two-theta.

The present invention also provides a process for preparing oxcarbazepine Form C comprising the steps of preparing a solution of oxcarbazepine and toluene, heating the solution, cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate, and separating the precipitate.

Oxcarbazepine is added to toluene to form a solution which is subsequently heated. Preferably, oxcarbazepine is added in an amount of from about 7.3 mg ml^{-1} to about 9.0 mg ml^{-1}, more preferably about 8.1 mg ml^{-1}. The solution is preferably heated to from about 25°C to about reflux, with temperatures at or near reflux being most preferred. One skilled in the art may appreciate that the solution may be completely homogeneous only after the heating step.

After heating for about 10 minutes, the solution is then cooled rapidly. The solution is cooled at a slower rate than is used to obtain Form B, but rapidly enough to allow for the formation of oxcarbazepine Form C as major product. Preferably, the solution is cooled at a rate of about 20°C to about 60°C per minute, and most preferably at a rate of about 40°C per minute. To cool the solution at a rate of 40C per minute, an ice water bath with a temperature of 0°C may be used,

The solution is preferably cooled to about 0°C. One skilled in the art may appreciate that other temperatures may also suffice as long as they allow for the substantial formation of Form C. After cooling, a precipitate forms, which is then separated. Preferably, the precipitate is separated with a filter. To filter, the solution may be passed through paper, glass fiber or other membrane materials, or a clarifying agent such as celite.

The present invention also provides oxcarbazepine Form D. Oxcarbazepine Form D is characterized by a PXRD pattern (Fig. 3) with peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

The present invention provides a process for preparing oxcarbazepine Form D comprising the steps of preparing a solution of oxcarbazepine in toluene, and evaporating the toluene from the solution.

Oxcarbazepine is first added to toluene to form a solution. Oxcarbazepine is preferably added in an amount of from about 8.5 to about 9.5 milligrams per gram of toluene, more preferably about 9.1 mg g^{-1}.

The solution is then preferably heated to completely dissolve the oxcarbazepine. The solution is preferably refluxed for a short amount of time, about five minutes, though a different of temperature and amount of time may also achieve the same result. One skilled in the art may appreciate that the solution may become completely homogeneous only after the heating step.

After heating, the solution is then preferably cooled to decrease the solubility of oxcarbazepine in the toluene. The solution is cooled at a slower rate than the processes resulting in Forms B and C. The solution is cooled at a rate of 20°C min^{-1} and below, more preferably at a rate of about 10°C min^{-1} to about 20°C min^{-1}, and most preferably at a rate of 15°C min^{-1}. The solution is cooled in such a way that a precipitate does not substantially form during cooling.

The solution is preferably cooled to from about 0°C to about room temperature, most preferably to about 0°C. One skilled in the art may appreciate that other temperatures may achieve the same result.

After cooling, the toluene is removed by evaporation. The toluene may be evaporated under ambient or reduced pressure, or optionally heated to accelerate the evaporation. After evaporation, a residue remains which PXRD analysis has confirmed is oxcarbazepine Form D.

The process for the preparation of Form B in Example 1 and the process for the preparation of Form D are similar. To prepare Form D, oxcarbazepine is first added to toluene and then the toluene is evaporated. To prepare Form B, oxcarbazepine is first dissolved in dichloromethane and is added to toluene as a solution. The mixed solvent is then removed by evaporation to obtain Form B.

The present invention also provides oxcarbazepine as a solvate of chloroform. The oxcarbazepine solvate of the present invention is characterized by a PXRD pattern (Fig. 4) with peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta. More particularly, the present invention provides for oxcarbazepine chloroform solvate Form E.

This form contains about 27% solvent, which corresponds to a ¾ solvate of chloroform. The solvent content was measured by TGA, and a weight loss of 27% was seen between 30°C and 90°C. This desolvatation is also observed in the DSC as an endotherm in the temperature range of about 40°C to 90°C.

The present invention also provides a process for preparing oxcarbazepine solvate Form E comprising causing formation of a precipitate from a solution of oxcarbazepine and chloroform, and separating the precipitate. The conditions used are different than that of producing Form A by crystallization from chloroform, for instance dissolution at reflux and cooling at 10°C min^{-1} rate.

Oxcarbazepine is first dissolved in chloroform to form a solution. Oxcarbazepine is preferably added in an amount of from about 6.8 to about 8.0 milligrams per gram of chloroform, more preferably about 7.3 mg g^{-1}. The solution is then preferably heated to increase the amount of oxcarbazepine taken up by the chloroform. Preferably, the solution is completely homogeneous after the heating step. The solution is preferably heated from about 50°C to about 60°C, and most preferably to about 55°C.

After heating, the solution is cooled. Preferably, the solution is cooled to a temperature at or below room temperature. Most preferably, the solution is cooled to about 16°C. The solubility of chloroform for oxcarbazepine decreases as the solution is cooled. To allow the solution to be cooled to a low temperature of about 16°C without premature precipitation, the solution may first be cooled to a first temperature, and after a while to a second, lower temperature. Preferably, the solution is first cooled to about 25°C, and then to below room temperature. After cooling, a precipitate forms. The precipitate may be separated using a filter. Before filtering, the solution may be allowed to warm. Preferably, the solution is warmed to about 25°C.

The present invention also provides for processes that convert one form of oxcarbazepine into another form of oxcarbazepine. Form A may be obtained by heating oxcarbazepine solvate Form E at elevated temperatures between 40°C and 80°C, preferably 60°C, for a period of 2 hours to 10 hours, preferably 4 hours. One skilled in the art may appreciate that Form E may transform to Form A under different conditions, and that the optimal conditions may be discovered with routine experimentation.

The present invention also provides a process for transforming Form B to Form C. It was found that Form B transforms to Form C at from about 20 to about 30°C, *i.e.* at about room temperature. The transformation is gradual and prolonged, and may occur over several months. One skilled in the art may appreciate that the optimal conditions and time for transformation may be discovered through routine experimentation.

The present invention also provides a process for transforming Form B to Form A. At about ambient temperature, Form B transforms to Form C. One skilled in the art would appreciate that such a transition may also occur at temperatures above and below ambient temperature, and that by routine experimentation the boundary of the temperature range may be determined. At higher temperatures, between 60°C and 120°C, preferably 60°C, a transformation from form B to form A occurs after a few hours, as determined by the temperature. The temperature at which Form B transforms to Form A rather than Form C may be determined by routine experimentation. One skilled in the art may appreciate that the rate and extent of the transformation varies with the conditions and the amount of time under which the transformation occurs.

The present invention also provides a process for transforming Forms B, C, and D to Form A. It was found that Forms B, C or D may transform readily to the prior art Form A by slurry in protic solvents like ethanol or water for a period between several hours and several days, preferably for a period of 24 hours. One skilled in the art may appreciate that other protic solvents may be used and the optimal conditions may be determined through routine experimentation.

The pharmaceutical compositions of the present invention have valuable therapeutic benefits and act as a central nervous system depressant. The pharmaceutical compositions of the present invention may be used to treat epilepsy by preventing or reducing the extent of seizures. The pharmacological benefit of the compositions is primarily exerted through the 10-monohydroxy metabolite of oxcarbazepine. In vitro studies indicate that the metabolite blocks voltage sensitive sodium channels, which results in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and dimunition of propagation of synaptic impulses. The phamaceutical compositions of the present invention may also be used to treat Parkinson's disease.

Pharmaceutical compositions of the present invention contain oxcarbazepine Form B, C, D and/or E, optionally in mixture with other Form(s), or amorphous oxcarbazepine and/or active ingredients. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition 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 care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelitinized 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®), 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®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution 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®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) 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 dixoide, 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 sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor 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, clopidogrel hydrogensulfate and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

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, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, 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, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin 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 hydroxy toluene, 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 guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, 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.

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 losenges, 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 gelatin and optionally contain a plasticizer such as glycerin 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 tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be 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 tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

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

The solid unit dosage forms of the present invention preferably contain about 150, 300 or 600 mg of oxcarbazepine. The unit dosage form as used herein refers to the amount of the various forms of oxcarbazepine contained in the vehicle of administration, such as a tablet or a capsule. Most preferably, the unit dosage form of the present invention is administered as a tablet.

The tablet of the present invention is preferably film-coated and contains the following inactive ingredients: colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc and titanium dioxide; yellow iron oxide.

The liquid unit dosage forms of the present invention contain about 300 mg of oxcarbazepine in a suspension with 5mL of liquid. Most preferably, the suspension is administered orally and has about 60mg of oxcarbazepine for every milliliter of liquid.

The oral suspension of the present invention preferably contains the following inactive ingredients: ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

The characterization of crystalline phases were performed using Phillips PW 1710 Diffractometer. Thermograviometric analysis (TGA) was produced using Mettler TG50 equipped with Mettler TC11 TA processor. Differential Scanning calorimetry (DSC) was performed using Mettler DSC 30 apparatus. FTIR spectra were recorded using Nicolet Avatar 360 spectrometer.

One skilled in the art may appreciate that other unit dosages may be made as necessary in a routine fashion.

EXAMPLES

Example 1

Preparation of Form B

Oxcarbazepine (0.15 g) was dissolved in dichloromethane (20 g) at room temperature. After complete dissolution, the solution was added to toluene (170 mL). After stirring for 5 minutes the solvent was evaporated at the rate of 5 g min^{-1} until dryness. The resulting material was analyzed by PXRD and found to be form B.

Example 2

Preparation of Form B

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 5 minutes the reaction mixture was cooled immediately to 0°C. After 5 minutes, the suspension was filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be Form B.

Example 3

Preparation of Form C

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 10 minutes the reaction mixture was cooled to 0°C at the rate of 40°C per minute. After 5 minutes, the suspension was filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be Form C.

Example 4

Preparation of Form D

Oxcarbazepine (0.3 g) was dissolved in toluene (33 g) at room temperature. After reflux for 5 minutes the reaction mixture was cooled to 0°C. After 5 minutes, the solvent was evaporated. The resulting material was analyzed by PXRD and found to be Form D.

Example 5

Preparation of solvated Form E

Oxcarbazepine (1.1 g) was dissolved in chloroform (150 g) at room temperature. After heating to about 55°C for 5 minutes the reaction mixture was cooled to 21.5°C, and after 8 hours the reaction mixture was cooled to 16°C. After 48 hours the suspension was heated to 25°C, and filtered under reduced pressure. The resulting material was analyzed by PXRD and found to be solvated form E.

Example 6

Preparation of Form A from Form E

Oxcarbazepine solvate Form E was heated to a temperature of 60°C and maintained at that temperature for 4 hours. The resulting material was analyzed by PXRD, which showed oxcarbazepine Form A .

Example 7

Preparation of Form A from Form B

Oxcarbazepine Form B was heated to a temperature of about 60°C and was maintained at that temperature for five hours. The resulting material was analyzed by PXRD, which showed oxcarbazepine Form A.

Example 8

Preparation of Form A from Form B

Oxcarbazepine Form B was suspended in ethanol for 24 hours. The product was analyzed by PXRD and determined to be Form A.

Example 9

Preparation of Form A from Form C

Oxcarbazepine Form C was suspended in ethanol for 24 hours. The product was analyzed by PXRD and determined to be Form A.

Example 10

Preparation of Form A from Form D

Oxcarbazepine Form D was suspended in water for 24 hours. The product is analyzed by PXRD and is determined to be Form A.

Example 11

Preparation of Form C from Form B

Oxcarbazepine Form B was stored at an ambient temperature. The resulting material was analyzed by PXRD and found to be Form C.

Having described the invention with reference to particular preferred embodiments and illustrated it with examples, those in the art may appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification.

CLAIMS

What is claimed is:

1. Oxcarbazepine Form B.

2. Oxcarbazepine having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 20.0, 23.0, 25.1 ± 0.2 degrees two-theta.

3. The oxcarbazepine of claim **2** having a PXRD diffraction pattern with peaks at about 11.9, 14.4, 17.7, 19.4, 20.0, 21.1, 23.0, 24.0, 24.4 ,25.1, 26.0 ± 0.2 degrees two-theta.

4. The oxcarbazepine of claim **3** having a PXRD diffraction pattern substantially as depicted in figure 1.

5. A process for preparing oxcarbazepine Form B comprising the steps of:
   a) preparing a solution of oxcarbazepine in a mixture of dichloromethane and toluene, and
   b) evaporating the toluene and the dichloromethane leaving Form B as a residue.

6. The process of claim **5**, wherein the solution is prepared by dissolving oxcarbazepine in dichloromethane and adding the dichloromethane to toluene.

7. The oxcarbazepine Form B prepared by the process of claim **5**.

8. A process for preparing oxcarbazepine Form B comprising the steps of:
   a) preparing a solution of oxcarbazepine in toluene;
   b) heating the solution;

c) cooling the solution at a rate of 60°C min^{-1} or above to cause formation of a precipitate; and

d) separating the precipitate.

9. The process of claim **8**, wherein the solution is heated to about reflux.

10. The process of claim **8**, wherein the solution is cooled to a temperature of about 0°C.

11. The oxcarbazepine Form B prepared by the process of claim **8**.

12. Oxcarbazepine Form C.

13. Oxcarbazepine characterized by PXRD peaks at about 11.7, 21.7, 23.2, 24.4 ± 0.2 degrees two-theta

14. The oxcarbazepine of claim **13** characterized by PXRD peaks at about 11.7, 17.0, 18.0, 21.7, 23.2, 24.4, 26.0 ± 0.2 degrees two-theta.

15. The oxcarbazepine of claim **14** characterized by a PXRD diffraction pattern substantially as depicted in figure 2.

16. A process for preparing oxcarbazepine Form C comprising the steps of:

a) preparing a solution of oxcarbazepine in toluene;

b) heating the solution;

c) cooling the solution at a rate of from about 20 to 60°C min^{-1} to cause formation of a precipitate; and

d) separating the precipitate.

17. The process of claim **16**, wherein the solution is cooled at a rate of about 40°C

per minute.

18. The process of claim **16**, wherein the solution is cooled to about 0°C.

19. The process of claim **16**, wherein the solution is heated to about reflux.

20. The oxcarbazepine Form C prepared by the process of claim **16**.

21. Oxcarbazepine Form D.

22. Oxcarbazepine characterized by PXRD peaks at about 11.7, 14.2, 24.3 ± 0.2 degrees two-theta.

23. The oxcarbazepine of claim **22** characterized by a PXRD diffraction pattern substantially as depicted in figure 3.

24. A process for preparing oxcarbazepine Form D comprising the steps of:
    a) preparing a solution of oxcarbazepine in toluene; and
    b) evaporating the toluene leaving a residue of oxcarbazepine Form D.

25. The process of claim **24**, further comprising a step of heating the solution before evaporating.

26. The process of claim **25**, wherein the solution is heated to about reflux.

27. The process of claim **25**, further comprising cooling the heated solution before evaporating.

28. The process of claim **27**, wherein the solution is cooled to about 0°C.

29. The process of claim **24**, further comprising a step of cooling the solution.

30. The process of claim **29**, wherein the solution is cooled to about 0°C.

31. The process of claim **24**, wherein the toluene is removed from the solution by evaporation.

32. The oxcarbazepine Form D prepared by the process of claim **24**.

33. An oxcarbazepine chloroform solvate.

34. Oxcarbazepine chloroform solvate Form E.

35. An oxcarbazepine chloroform solvate characterized by a PXRD pattern with peaks at about 14.5, 15.0, 18.2, 21.4, 22.9, 24.0, 25.8, 26.0 ± 0.2 degrees two-theta.

36. The oxcarbazepine solvate of claim **35** characterized by a PXRD diffraction pattern substantially as depicted in figure 4.

37. The oxcarbazepine chloroform solvate of claim **33** containing about a 27 weight % chloroform.

38. A process for preparing oxcarbazepine chloroform solvate comprising:
    a) causing formation of a precipitate from a solution of oxcarbazepine in chloroform, and
    b) separating the precipitate.

39. The process of claim **38**, further comprising a step of heating the solution before causing formation of the precipitate.

40. The process of claim **39**, further comprising a step of cooling the heated solution, whereby cooling causes formation of the precipitate.

41. The process of claim **39**, wherein the solution is heated to an elevated temperature of from about 50°C to about 60°C.

42. The process of claim **41**, wherein the solution is heated to an elevated temperature of about 55°C.

43. The process of claim **41**, wherein the heated solution is cooled to a reduced temperature of from about 10°C to about 20°C.

44. The process of claim **43**, wherein the reduced temperature is about 16°C.

45. The oxcarbazepine chloroform solvate produced by the process of claim **37**.

46. A process for preparing oxcarbazepine Form A comprising:
    a) providing oxcarbazepine chloroform solvate Form E,
    b) heating the oxcarbazepine chloroform solvate, and
    c) recovering oxcarbazepine as Form A.

47. The process of claim **46**, wherein the oxcarbazepine solvate Form E is heated to an elevated temperature in the range of from about 40°C to about 80°C.

48. The process of claim **47**, wherein the elevated temperature is about 60°C.

49. A process for preparing oxcarbazepine Form A comprising
    a) providing oxcarbazepine Form B,
    b) heating the oxcarbazepine, and

c) recovering the oxcarbazepine as Form A.

50. The process of claim **49**, wherein oxcarbazepine Form B is heated to an elevated temperature in the range of from about 60°C to about 120°C.

51. The process of claim **50**, wherein the elevated temperature is about 60°C.

52. A process for the preparation of oxcarbazepine Form C comprising
a) providing oxcarbazepine Form B,
b) maintaining the oxcarbazepine at a temperature in the range of from about 20 to about 30°C, and
c) recovering the oxcarbazepine as Form C.

53. A process for preparing oxcarbazepine Form A comprising:
a) contacting oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C and oxcarbazepine Form D with a protic solvent; and
b) recovering oxcarbazepine as Form A.

54. The process of claim **53**, wherein the forms of oxcarbazepine are suspended in the protic solvent.

55. The process of claim **53**, wherein the protic solvent is selected from the group consisting of water and ethanol.

56. The process of claim **54**, wherein the oxcarbazepine is suspended in the protic solvent from about two hours to about three days.

57. The process of claim **56**, wherein the oxcarbazepine is suspended for about one day.

58. A pharmaceutical composition comprising:
    a) oxcarbazepine selected from the group consisting of oxcarbazepine Form B, oxcarbazepine Form C, oxcarbazepine Form D and oxcarbazepine Form E; and
    b) a pharmaceutically acceptable excipient.

59. The pharmaceutical composition of claim **58**, wherein the composition is mixed with one or more forms of oxcarbazepine.

60. A pharmaceutical dosage form comprising the pharmaceutical composition of claim **58**.

61. The pharmaceutical dosage form of claim **60**, wherein the dosage form is a capsule or tablet.

62. The pharmaceutical dosage form of claim **61**, wherein the dosage form is a tablet.

63. The pharmaceutical dosage form of claim **60**, containing a unit dosage of about 150mg to about 600mg oxcarbazepine.

64. The pharmaceutical dosage form of claim **63**, containing a unit dosage selected from the group consisting of about 150mg, 300mg and 600mg.

65. The pharmaceutical dosage form of claim **60**, wherein the dosage form is an oral suspension.

66. The pharmaceutical dosage form of claim **65**, wherein the dosage is about 60mg ml^{-1}.

67. The pharmaceutical dosage form of claim **66**, wherein the dosage is about 300mg ml^{-1}.

68. A method of preventing or reducing the severity of seizures comprising administrating the pharmaceutical composition of claim **58**.

69. The method of claim **68**, wherein the seizures are associated with epilepsy.

70. A method of treating Parkinson's disease comprising administrating the pharmaceutical composition of claim **58**.

71. A method of depressing the central nervous system comprising administering the pharmaceutical composition of claim **58**.

72. The method of claim **71**, wherein the central nervous system is depressed by blocking voltage sensitive sodium channels.

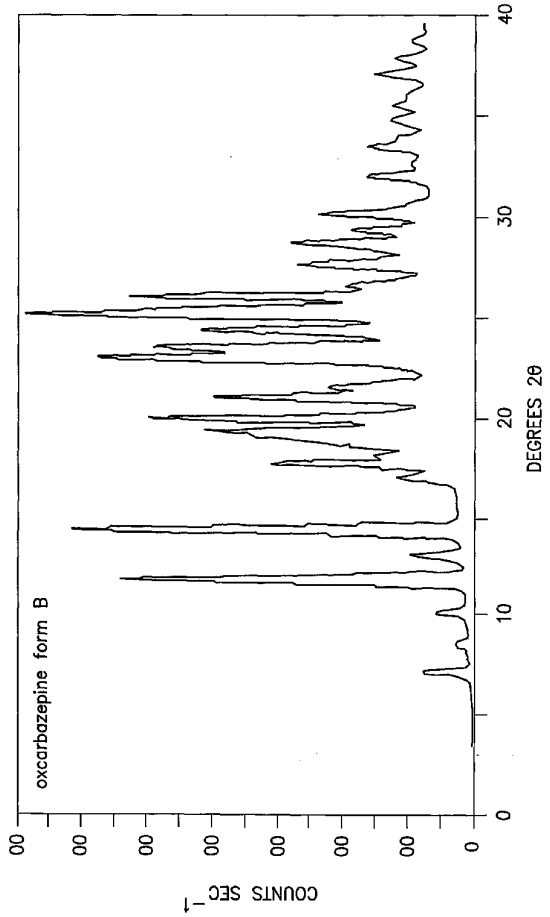


Fig. 1

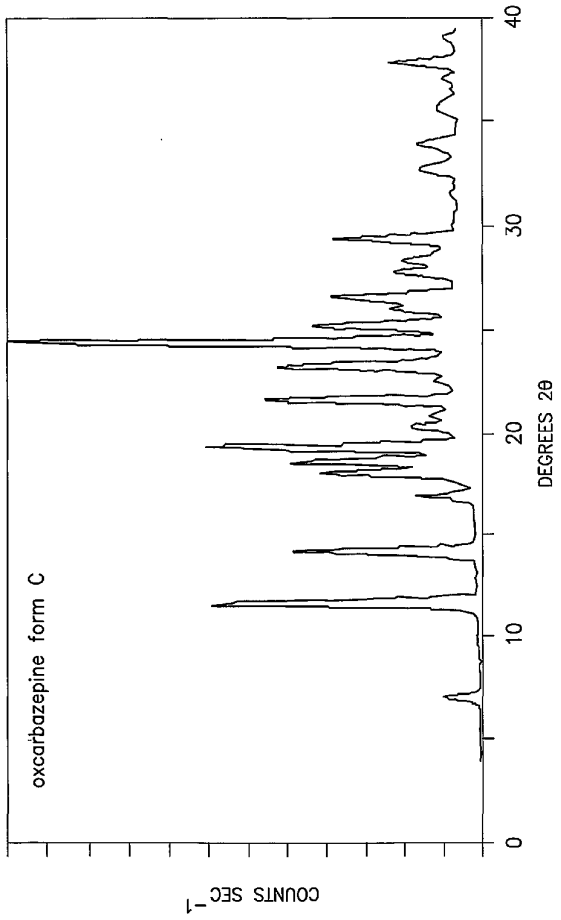


Fig. 2

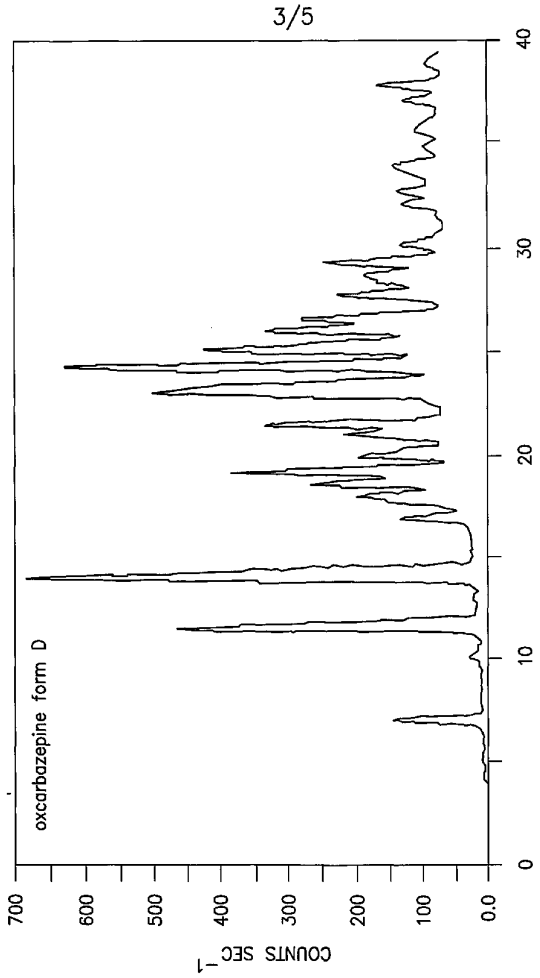
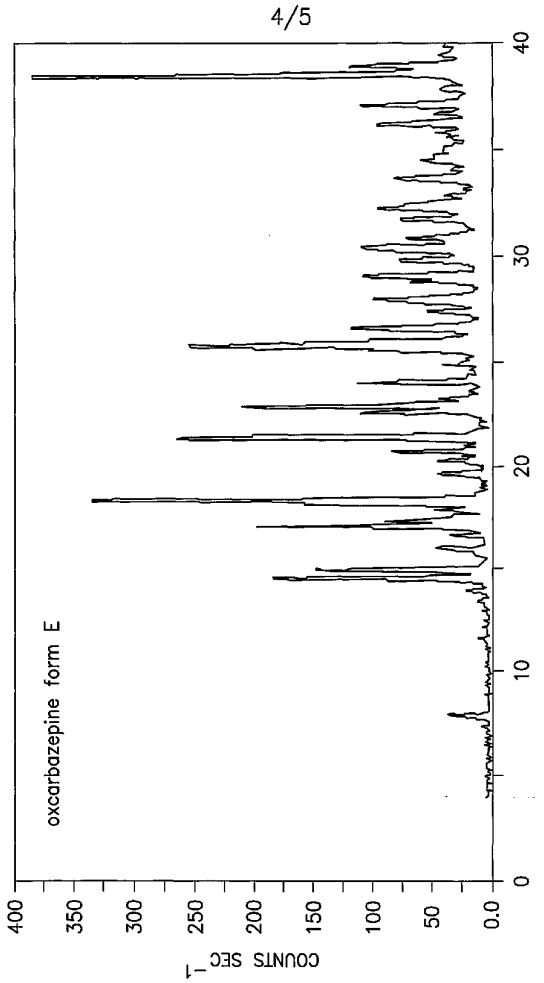

oxcarbazepine form D
COUNTS SEC^{-1}
700
600
500
400
300
200
100
0.0
0
10
20
30
40
DEGREES 2θ

Fig. 3


oxcarbazepine form E
COUNTS SEC^{-1}
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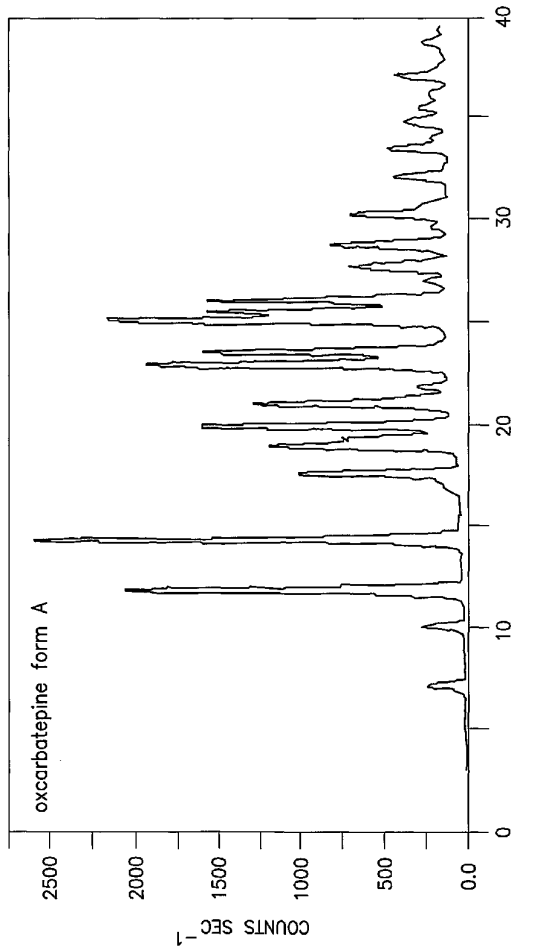
300
250
200
150
100
50
0.0
0
10
20
30
40
DEGREES 2θ

Fig. 4


oxcarbatepine form A
COUNTS SEC^{-1}
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2000
1500
1000
500
0.0
0
10
20
30
40
DEGREES 2θ

Fig. 5

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/04065

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 223/18; A61K 31/55; A61P 25/08
US CL : 514/217; 540/588
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)
U.S. : 514/217; 540/588

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)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,716,640 A (SCHINDLER) 13 February 1973 (13.02.1973).	1-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2002 (12.07.2002)	08 AUG 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Brenda L. Coleman Telephone No. 703-308-1235

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(74)代理人 100082898
弁理士 西山 雅也
(72)発明者 アロンハイム，ジュディス
イスラエル国，７６２１７ レホボット，レホブ ハラブ マオー イオセフ ５エー
(72)発明者 ドリツキー，ベンージオン
イスラエル国，ペタチ ティクバ，ロハメ ハゲット ３２
(72)発明者 ベルコビチ，ヤナ
イスラエル国，９３９０２ エルサレム，ハーアナファ ストリート ３０９／２０
(72)発明者 ガース，ニッシム
イスラエル国，ラモット ９７２７８，デレチ アコレシュ ストリート ９

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