Title: PROCESS AND PRODUCT

Abstract: A process of preparing topiramate of the formula (I) which comprises the following reaction steps and topiramate prepared thereby, compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.
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PROCESS AND PRODUCT

The present invention is concerned with a process of preparing topiramate, highly pure topiramate prepared thereby, compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

Topiramate is a sulfamate – substituted monosaccharide, described chemically as 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate. Topiramate has the following structural formula:

![Structural formula of topiramate]

Topiramate is an anti-epileptic drug, which is not chemically related to other known anticonvulsant and / or antiepileptic drugs, or mood regulating medication. Topiramate can be particularly useful in demonstrating efficacy of treatment in respect of the treatment of patients who have not responded to other anticonvulsant drugs or medications. Topiramate is also distinctive in its side-effect profile, and is further distinctive in its ability to substantially control rapid cycling and mixed polar states in patients who do not benefit from other known drugs, such as carbamazepine, sodium valproate and the like.

Topiramate and processes for the preparation thereof have been disclosed and claimed in US 4513006. US 4513006 discloses a number of distinct synthetic routes. One of the general methods disclosed provides for a method of reacting 2,3,4,5-bis-O-(1-isopropylidene)-β-D-fructopyranose with sulfuryl chloride to obtain a chlorosulfate compound, which is then reacted with sodium azide to give the sulfamoyl azide. The azide is then reduced using either copper-methanol or hydrogenated to obtain the
sulfamate. There is no specific teaching in US 4513006 of topiramate prepared by the above synthetic route. Following the specific preparation details for topiramate disclosed in US 4513006, a very impure product is obtained. More particularly, US 4513006 discloses the reaction of 2,3:4,5-bis-O-(1-isopropylidene)-β-D-fructopyranose with sulfamoyl chloride to obtain topiramate. Sulfamoyl chloride is not very reactive, requires a strong base to carry out the reaction and furthermore is not readily available.

US 5387700 claims a purification process for topiramate using alcohol and water, or ethyl acetate/hexane. The product obtained by such purification process is unstable and has a short shelf-life.

A. Klockow-Beck et.al. in J. Chromatogr. B, 720 (1998) 141-151, have reported that topiramate is highly unstable under conditions of elevated temperature and humidity, giving organic degradation products, insoluble polymeric products and inorganic sulfate and sulfamate anions.

Topiramate prepared according to the teaching of the prior art thus suffers from instability problems and also exhibits a very short shelf life. As such, it has been difficult to formulate and store topiramate prepared further to the teaching of the prior art, with storage conditions required to be below ambient conditions or under refrigeration. The instability associated with prior art topiramate has been attributed to the presence of impurities in the final drug compound, which could at least in part be attributable to isolation thereof from a methanolic solution.

There is, therefore, a need for a process of preparing topiramate that exhibits improved purity, which can be stored at ambient conditions for extended periods, and does not degrade during its shelf life and thus is suitable for formulation in dosage form.

According to the present invention, therefore, there is provided a process of preparing topiramate of following formula (I)
wherein said topiramate of formula (I) is prepared by hydrogenation of a precursor azide of formula (II)

\[ \text{(II)} \]

The above hydrogenation step is typically carried out in the presence of a noble metal catalyst, such as palladium on charcoal, suitably using ethyl acetate as solvent, to obtain topiramate of formula (I) which is substantially free from impurities and degradation products associated with prior art processes. Furthermore, use of ethyl acetate as a solvent for the above hydrogenation according to the present invention is also preferable for a safety aspect as compared to use of methanol as taught by US 4513006. The hydrogenation is typically carried out at a pressure in the range of about 1 to 10 bar, and suitably at a temperature in the range of about ambient to 70°C. After hydrogenation, the catalyst is filtered off and the filtrate is subjected to prolonged treatment with activated charcoal or other suitable adsorbents such as silica gel or alumina or diatomaceous earth substantially as hereinafter described. This purified product is isolated by known methods such as by chilling or addition of a non-solvent such as hexane, followed by filtration.

A precursor azide compound of formula (II) as shown above is in turn suitably prepared from an intermediate chlorosulfate of formula (III)
typically by reaction of the chlorosulfate of formula (III) with sodium azide. The resulting azide compound of formula (II) is preferably purified by dissolving the crude product in dichloromethane and washing with water to remove impurities and trace degradation products, which could otherwise be carried over to the final product.

An intermediate chlorosulfate of formula (III) can in turn suitably be prepared by reaction of sulfuryl chloride with 2,3:4,5-bis-O-(1-isopropylidene)-β-D-fructopyranose of following formula (IV)

2,3:4,5-bis-O-(1-isopropylidene)-β-D-fructopyranose can be readily prepared by methods known in the art, for example by reacting fructose with acetone in the presence of concentrated sulphuric acid at room temperature.

A process according to the present invention can also be represented by the following reaction scheme
The reaction conditions for each of the above process steps in the overall scheme are as hereinbefore described for the respective steps.

A process of preparing topiramate according to the present invention typically further comprises purification of topiramate by recrystallization from isopropanol. The isopropanol used for the purification is substantially free of moisture, for example has a moisture content of less than 0.5%. The product, which is subjected to recrystallization
from isopropanol, may be a crude product directly obtained further to the above reaction steps, or may have previously been subjected to an initial purification, in either ethyl acetate or isopropanol. The initial purification is essentially carried out to substantially eliminate unreacted d-fructose, and / or bis-isopropylidene impurities of the following formulae (V) and (VI)

![Chemical structures](image)

where R is Cl or N₃.

Further purification can comprise dissolving topiramate in isopropanol at elevated temperatures, for example at about 50 to 60°C and optionally carrying out prolonged treatment with activated charcoal, silica gel and / or alumina in order to facilitate the preferential adsorption of the sulfate and sulfamate degradation products on the adsorbents. Topiramate obtained by such purification is substantially free of the degradation products such as sulfates and sulfamates as described by A. Klockow-Beck et.al. The typical level of degradation products and impurities associated with topiramate prepared by a process of this invention is less than about 0.2%, and more preferably less than about 0.1%.

A process according to the present invention provides topiramate, which is substantially more stable under conditions of normal storage, and thus exhibits a longer shelf-life as compared to topiramate obtained from processes known in the art. For example, topiramate prepared by process of the present invention is stable for more than 3 years under conditions of normal storage as compared to about 2 years for topiramate produced by prior art methods. Topiramate provided by the process of the present invention contains negligible amounts of degradation products, even when approaching the end of its shelf life. Furthermore, under conditions of accelerated stability, i.e., at 40±2°C and 75% relative humidity, topiramate according to the present invention is
stable for a period of not less than 6 months, whereas prior art topiramate degrades rapidly and turns brown, indicating the formation of polymeric degradation products.

There is provided by the present invention, therefore, topiramate prepared by a process substantially as hereinbefore described.

There is further provided by the present invention topiramate which includes degradation and / or impurities at a level of less than about 0.2%, and more preferably less than about 0.1%. Suitably the degradation products and / or impurities include unreacted d-fructose, and / or bis-isopropylidene impurities of the following formulae (V) and (VI)

\[
\text{(V)} \quad \text{O} \quad \text{H} \quad \text{O} \\
\text{H} \quad \text{O} \quad \text{H} \\
\]

\[
\text{(VI)} \quad \text{O} \quad \text{SO}_2\text{R} \\
\text{O} \quad \text{O} \\
\]

where R is Cl or N\textsubscript{3}, and / or degradation products including sulfates and sulfamates. Topiramate as provided by the present invention can be further characterised by the above described stability under storage conditions again as described above.

As indicated above, topiramate is useful as an anticonvulsant and is particularly useful in the treatment of epilepsy. There is further provided by the present invention, therefore, a pharmaceutical composition comprising an effective epilepsy inhibiting amount of topiramate, together with a pharmaceutically acceptable carrier, diluent or excipient therefor. To prepare the pharmaceutical compositions of this invention, topiramate is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like;
for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed and in particular the preferred dosage form are tablets as described in further detail in the accompanying examples. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

The pharmaceutical compositions described herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful, suppository and the like, from about 10 to about 500 mg of the active ingredient.

There is also provided by the present invention topiramate as provided by the present invention substantially as hereinbefore described, for use in therapy.

The present invention further provides topiramate provided by the present invention for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of an anticonvulsant, in particular for the manufacture of a medicament for the treatment of epilepsy.

The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of an anticonvulsant in a patient in need of such treatment, especially epilepsy, which method comprises administering to the patient a therapeutically effective amount of topiramate as provided by the present invention substantially as hereinbefore described.

The process of the present invention is now further illustrated by the following examples, which in no way limit the scope of the invention.

**Examples**

**Example 1**

2,3:4,5-Bis-O-(1-isopropyldene)-β-D-Fructopyranose Sulfamoyl azide
To methylene chloride (400ml) and triethylamine (86ml), 2,3:4,5-bis-O-(1-isopropylidene)-β-D-fructopyranose (80gm) was charged and stirred to obtain a clear solution. The reaction mass was cooled to –10 °C. Sulfuryl chloride (70gm) was added slowly under stirring, whilst maintaining a temperature at –10°C to –5°C. After the addition was complete, the stirring was continued for 30 minutes. The reaction mass was quenched in water (400ml) under stirring below 10°C. The aqueous layer was extracted with methylene chloride (80ml). The organic layer was washed with water (400ml) and then concentrated under vacuum below 40°C to almost residue. Acetonitrile (80ml) was charged and distillation continued below 40°C for complete removal of methylene chloride. An additional quantity of acetonitrile (400ml) was charged to the residue under stirring and cooled to 25 – 30 °C and sodium azide (44.8gm) was charged under nitrogen atmosphere followed by pyridine (51.2ml). The reaction mass was stirred at 25 – 30°C for 14 hours. After the reaction was completed, water (1200ml) was added slowly to the reaction mass, which was stirred for 2 hours, filtered and washed with water (200ml).

The wet cake was dissolved in methylene chloride (400ml) and washed with water. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride (250ml). The combined methylene chloride extract was concentrated under vacuum below 40°C to a residue. Isopropyl alcohol (150ml) was charged to the residue and distillation continued to remove methylene chloride completely. The concentrated mass was then chilled to 5 – 10°C under stirring. The product was filtered and washed with isopropyl alcohol (20ml).

The wet cake was dried under vacuum at 35 – 40 °C (Yield : 75gm).

Example-2

2,3:4,5-Bis-O-(1-isopropylidene)-β-D-Fructopyranose sulfamate

To ethyl acetate (450ml), 2,3:4,5-Bis-O-(1-isopropylidene)-β-D-fructopyranose sulfamoyl azide (60gm) obtained further to Example 1 was charged under stirring to obtain a clear solution. To this clear solution, 5% palladium carbon catalyst (8.25gm) slurry in ethyl acetate (60ml) was charged and hydrogen gas was passed to attain a
pressure of 55 – 60 psi and maintained for 8 hours. After the reaction was complete, the reaction mass was filtered to obtain a clear solution.

The clear filtrate was charcoalised at 25 – 30°C for 6 hours and was filtered over Hyflo bed and washed with ethyl acetate (100ml). The washings were also collected with the main filtrate. The clear filtrate was washed with water (18ml) and the organic layer was dried over anhydrous sodium sulfate. The ethyl acetate layer was filtered and the clear filtrate was concentrated under vacuum at a temperature below 45°C to a residue. Isopropyl alcohol (30ml) was added and distillation continued to remove ethyl acetate. An additional quantity of isopropyl alcohol (30ml) was added, cooled to 25 – 30°C followed by n-hexane (120ml) addition. The product was isolated by chilling the reaction mass to 5 – 10°C, filtered and washed with n-hexane (25ml).

The wet cake was dissolved with isopropyl alcohol (200ml) at 55 – 60°C. The reaction mass was chilled to 10 – 15°C and maintained for 1 hour. It was then filtered and washed with isopropyl alcohol (20ml).

The product was dried at 40 – 45°C under vacuum (Yield :34.3 gm).

Example 3

Tablet formulation

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Topiramate</td>
<td>100.00</td>
</tr>
<tr>
<td>2.</td>
<td>Pregelatinised Starch</td>
<td>3.50</td>
</tr>
<tr>
<td>3.</td>
<td>Lactose monohydrate</td>
<td>99.00</td>
</tr>
<tr>
<td>4.</td>
<td>Microcrystalline Cellulose</td>
<td>96.50</td>
</tr>
<tr>
<td>5.</td>
<td>Sodium Starch Glycolate (Primojel)</td>
<td>18.00</td>
</tr>
<tr>
<td>6.</td>
<td>Magnesium stearate</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>CORE WEIGHT</td>
<td>320.00</td>
</tr>
<tr>
<td>7.</td>
<td>Purified water usp</td>
<td>q.s.</td>
</tr>
<tr>
<td>8.</td>
<td>Opadry Beige TS-1-17174-A</td>
<td>12.00</td>
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<tr>
<td>TOTAL TABLET WEIGHT</td>
<td>332.00</td>
<td></td>
</tr>
</tbody>
</table>
CLAIMS

1. A process of preparing topiramate of following formula (I)

(I)

wherein said topiramate of formula (I) is prepared by hydrogenation of a precursor azide of formula (II)

(II)

2. A process according to claim 1, wherein said hydrogenation is carried out in the presence of palladium on charcoal.

3. A process according to claim 1 or 2, wherein ethyl acetate is employed as a solvent.

4. A process according to any of claims 1 to 3, wherein said hydrogenation is carried out at a pressure in the range of about 1 to 10 bar.

5. A process according to any of claims 1 to 4, wherein said hydrogenation is carried out at a temperature in the range of about ambient to 70°C.
6. A process according to any of claims 1 to 5, wherein said precursor azide compound of formula (II) is prepared from an intermediate chlorosulfate of formula (III)

![Chemical Structure](image)

(III)

by reaction of the chlorosulfate of formula (III) with sodium azide.

7. A process according to claim 6, wherein the resulting azide compound of formula (II) is purified by dissolving in dichloromethane and washing with water.

8. A process according to claim 6 or 7, wherein said chlorosulfate of formula (III) is prepared from 2,3:4,5-bis-O-(1-isopropyldene)-β-D-fructopyranose of following formula (IV)

![Chemical Structure](image)

(IV)

by reaction of said 2,3:4,5-bis-O-(1-isopropyldene)-β-D-fructopyranose of formula (IV) with sulfuryl chloride.

9. A process of preparing topiramate of the formula (I) which comprises the following reaction steps
10. A process according to any of claims 1 to 9, which further comprises purification of topiramate of formula (I) by recrystallization from isopropanol.

11. A process according to claim 10, wherein said isopropanol is substantially free of moisture.
12. A process according to any of claims 1 to 11, which further comprises initial purification in either ethyl acetate or isopropanol.

13. A process according to claim 12, wherein said initial purification is carried out to substantially eliminate unreacted d-fructose and / or bis-isopropylidene impurities of the following formulae (V) and (VI)

![Formula (V)](image)

![Formula (VI)](image)

where R is Cl or N₃.

14. A process according to any of claims 1 to 13, which further comprises treatment of topiramate with activated charcoal, silica gel and / or alumina in order to facilitate preferential adsorption of sulfate and sulfamate degradation products on these adsorbents.

15. A process of preparing topiramate of following formula (I)

![Formula (I)](image)

which includes purification in either ethyl acetate or isopropanol to substantially eliminate the presence of unreacted d-fructose and / or bis-isopropylidene impurities of the following formulae (V) and (VI)
where R is Cl or N\textsubscript{3}.

16. A process of preparing topiramate of following formula (I)

which includes treatment of topiramate with activated charcoal, silica gel and / or alumina in order to facilitate preferential adsorption of sulfate and sulfamate degradation products on these adsorbents.

17. A process according to any of claims 1 to 16, wherein the level of degradation products and / or impurities associated with topiramate prepared thereby is less than about 0.2%.

18. A process according to claim 17, wherein the level of degradation products and / or impurities associated with topiramate prepared thereby is less than about 0.1%.

19. A process according to any of claims 1 to 18, wherein topiramate prepared thereby is stable for more than 3 years under conditions of normal storage.
20. A process according to any of claims 1 to 19, wherein topiramate prepared thereby, under conditions of accelerated stability of 40±2°C and 75% relative humidity, is stable for a period of not less than 6 months.

21. Topiramate prepared by a process according to any of claims 1 to 20.

22. Topiramate which includes degradation and / or impurities at a level of less than about 0.2%.

23. Topiramate which includes degradation and / or impurities at a level of less than about 0.1%.

24. Topiramate according to claim 22 or 23, wherein said degradation products and / or impurities include unreacted d-fructose and / or bis-isopropylidene impurities of the following formulae (V) and (VI)

\[ \text{(V)} \]

\[ \text{(VI)} \]

where R is Cl or N₃, and / or degradation products including sulfates and sulfamates.

25. Topiramate which is stable for more than 3 years under conditions of normal storage.

26. Topiramate which under conditions of accelerated stability of 40±2°C and 75% relative humidity, is stable for a period of not less than 6 months.
27. A pharmaceutical composition comprising an effective epilepsy inhibiting amount of topiramate according to any of claims 21 to 26, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

28. Topiramate according to any of claims 21 to 26, for use in therapy.

29. Topiramate according to any of claims 21 to 26, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of an anticonvulsant.

30. A method of treating a disease state prevented, ameliorated or eliminated by the administration of an anticonvulsant in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of topiramate according to any of claims 21 to 26.