Title: TROMETHAMINE SALT OF VALPROIC ACID

Abstract: An improved valproic acid salt, the tromethamine salt of valproic acid (TRIS-valproate) is disclosed. TRIS-valproate provides superior stability, storage, tabletting and patient tolerance. A crystalline form of TRIS-valproate, a method of making TRIS-valproate, as well as pharmaceutical dosage forms and methods of treating patients comprising TRIS-valproate are also disclosed.
TROMETHAMINE SALT OF VALPROIC ACID

BACKGROUND OF INVENTION

The present invention relates to a novel tromethamine salt of valproic acid, a method for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the crystalline tromethamine salt of valproic acid.

The drug substance valproic acid, or 2-propylpentanoic acid, is known for its anticonvulsant properties. Valproic acid is commonly used in the treatment of epileptic seizures and convulsions, as well as for treating bipolar disorders. Valproic acid is a colorless clear liquid which is lightly soluble in water. Oral formulations of valproic acid are therefore inconvenient to prepare and difficult to dispense.

The sodium salt of valproic acid, sodium valproate, is a white crystalline powder. Unfortunately, because of its high degree of hygroscopicity, sodium valproate is difficult to handle and process, resulting in difficulties in storage and tablet formulation. Further, the free acid and the sodium salt frequently cause adverse GI effects such as nausea, vomiting and indigestion. For these reasons, both valproic acid and sodium valproate have limited utility in the preparation of oral dosage forms.

Abbott Laboratories has developed a hemi-sodium salt of valproic acid, known as divalproex sodium. Divalproex sodium, commercialized under the trade name Depakote®, is a slow polymeric compound consisting of valproic acid and valproate sodium in a 1:1 molar ratio, whose use is purported to reduce adverse GI effects.

Accordingly, the present invention is directed to developing valproic acid compositions that provide improved stability and tablet forming characteristics as well as exhibit improved patient tolerance.

SUMMARY OF INVENTION

The present invention relates to the novel tromethamine salt of valproic acid. In one aspect of the present invention a crystalline form of tromethamine salt of valproic acid is provided. The crystalline form is characterized by an x-ray diffraction pattern having characteristic scattering peaks expressed in units of degrees 2θ (± 0.2°) at 5.4, 6.4, 6.8, 8.1, and 21.5.

In another aspect of the present invention there is provided a method of making tromethamine salt of valproic acid, the method comprising dissolving the valproic acid in at least one solvent; adding the tromethamine to the at least one solvent to form a reaction mixture; and allowing the valproic acid and tromethamine to react to form the tromethamine salt of valproic acid.

In further aspects of the present invention, there are provided a pharmaceutical dosage form and a method of treating a patient with a pharmaceutical composition of tromethamine salt of valproic acid.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is an x-ray powder diffraction pattern of a crystalline form of tromethamine salt of valproic acid of the present invention.
[0010] Figure 2 is a differential scanning calorimetry thermogram of a crystalline form of valproic acid of the present invention.

[0011] Figure 3 is a Fourier-transform infrared absorption spectrum of a crystalline form of valproic acid of the present invention.

DETAILED DESCRIPTION

[0012] There is provided an improved salt of valproic acid, the valproic acid salt (hereinafter TRIS-valproate.) Tromethamine (2-Amino-2-(hydroxymethyl)-1,3-propanediol or tris(hydroxymethyl)aminomethane [77-58-1]) is also commonly referred to as TRIS or TRIS buffer.

[0013] The TRIS-valproate of the present invention is a self-buffering compound possessing a high degree of water solubility. TRIS-valproate is easily manufactured, providing a highly crystalline form that is easily handled and dried, providing improved stability and tabling characteristics. The quality and purity of the TRIS-valproate of the present invention facilitates it being processed into drug dosage forms. The improved TRIS buffered salt disclosed herein results in less irritation of the GI tract as compared to valproic acid or the conventional sodium salt formulations.

[0014] In another aspect, the invention provides a crystalline form of TRIS-valproate. The crystalline form of TRIS-valproate has been characterized by powder X-ray diffraction ("PXRD") analysis, by differential scanning calorimetry ("DSC") and Fourier-transform infrared absorption ("FT-IR").

[0015] The PXRD pattern for the crystalline form of TRIS-valproate of the present invention is depicted Figure 1. The scale of the region encompassing 12 to 37 degrees 2θ was multiplied by a factor of 4.0 in Fig. 1. The scattering angles and d-spacings in the PXRD pattern for the crystalline form of TRIS-valproate are given in Table 1, below:
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<tr>
<th>Scattering Angle (degrees 2θ)</th>
<th>d-Spacing (Å)</th>
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<tbody>
<tr>
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<td>32.5</td>
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The PXRD pattern was obtained using a Rigaku MiniFlex powder diffraction system, equipped with a horizontal goniometer in the θ / 2θ mode. The x-ray source was nickel-filtered Kα emission of copper (1.55314 Å). Samples were packed into an aluminum holder using a back-fill procedure, and were scanned over the range of 6 to 48 degrees 2θ, at a scan rate of 0.5 degrees 2θ/min. Using a data acquisition rate of 1 point per second, the scanning parameters equate to a step size of 0.0084 degrees 2θ. Calibration of each powder pattern was effected using the characteristic scattering peaks of aluminum at 44.738 and 38.472 degrees 2θ, so the useful range for sample characterization range was 6 to 36 degrees 2θ.

The crystalline form of TRIS-valproate was further characterized by DSC (Figure 2). Fig. 2 possesses a sharp melting endotherm with an onset temperature of 55.6°C and a maximum at 57.8°C. Due to differences in equipment and rate of heating, among other things, TRIS-valproate that produces a thermal analysis result, e.g. measured melting point, maximum melting endotherm, inflection point in heat absorption curve and the like, that is indicative of melting at about 55°C to about 60°C is consistent with its identity as depicted in Fig. 2. The enthalpy of fusion was determined to be 130.5 J/g⁻¹.

DSC was performed using a TA Instruments 2910 thermal analysis system. Samples of approximately 1-2 mg were accurately weighed into an aluminum DSC pan, and covered with an
aluminum lid that was clamped in place. The samples were then heated over the range of 25°C to 240°C, at a heating rate of 10°C/min.

[0020] An FT-IR absorption spectrum, shown in Figure 3, was obtained at a resolution of 2 cm⁻¹ using a Shimadzu model 8400 FT-IR spectrometer, and represents the averaging of 25 interferograms. The data were acquired using the attenuated total reflectance sampling mode, where the samples were clamped against the ZnSe crystal of a Pike MIRacle™ single reflection horizontal ATR sampling accessory. Absorption bands characteristic of the TRIS-valproate compound were observed at 1059, 1535, and 1586 cm⁻¹.

[0021] In an illustrative, non-limiting method of production, valproic acid is dissolved in at least one solvent while stirring. Suitable solvents include any pharmaceutically acceptable non-reactive solvent into which the valproic acid dissolves, including but not limited to alcohols such as methanol, ethanol, propanol and mixtures thereof. In a preferred, non-limiting embodiment, an equimolar amount of tromethamine is added, and the resulting reaction mixture is stirred until the reaction is substantially complete, typically about 30 to about 60 minutes at room temperature. The reaction is not temperature sensitive, with a suitable temperature range from about 30°C to about 90°C. The alcohol is then removed under vacuum to yield the TRIS-valproate.

[0022] The TRIS-valproate of the present invention is suitable for use as an active pharmaceutical ingredient (API) in a pharmaceutical composition. Illustrative, non-limiting uses of the TRIS-valproate are for treating patients suffering from epileptic seizures and/or convulsions, as well as for the treatment of bipolar disorders. The TRIS-valproate is typically administered to the patient using a solid dosage form, with a tablet or capsule being presently preferred. Pharmaceutical compositions in solid dosage form may include tablets, powders, capsules, suppositories, sachets, troches and lozenges. However, it is noted that the TRIS-valproate of the present invention may be administered in any suitable dosage form, by any suitable method without limitation.

[0023] The following example is given for illustrative purposes only and is not intended to limit the invention as disclosed herein or the appended claims in any way.

EXAMPLE

[0024] Valproic acid (5.6 g, 40 mmol, 100 mol %) was added to methanol (50 mL) and stirred until the valproic acid was substantially dissolved. Tris(hydroxymethyl)aminomethane (4.8 g, 40 mmol, 100 mol %) was then added and the resulting mixture was stirred for 30 minutes at room temperature. The methanol was removed under vacuum at 180 mbar at 80°C. The isolated product is crystalline, and has a melting point of about 65°C to about 66°C. The product (10.1 g, 97% yield) was determined to be TRIS-valproate.

[0025] The product was characterized by PXRD, which was consistent with that shown in Fig. 1, by DSC, which was consistent with Fig. 2, and by FT-IR, which was consistent with Fig. 3.

Elemental Analysis

[0026] The calculated and empirically determined elemental analyses for the anhydrous tromethamine salt of valproic acid are as follows and as in Table 2:

Empirical formula = C₉H₁₇NO₄

Molecular weight = 265.35
Having described the invention in detail, those skilled in the art will appreciate that modifications may be made of the invention without departing from its spirit and scope. Therefore, it is not intended that the scope of the invention be limited to the specific embodiments described. Rather, it is intended that the appended claims and their equivalents determine the scope of the invention.
We claim:

1. Tromethamine salt of valproic acid.
2. A crystalline form of the tromethamine salt of valproic acid.
3. The crystalline form of tromethamine salt of valproic acid of Claim 2 characterized by an X-ray diffraction pattern having characteristic peaks expressed in degrees 2θ (± 0.2°) at 5.4, 6.4, 6.8, 8.1, and 24.5.
4. The crystalline form of tromethamine salt of valproic acid of Claim 2 characterized by an X-ray diffraction pattern having characteristic peaks expressed in degrees 2θ (± 0.2°) at 5.4, 6.4, 6.8, 7.3, 8.1, 8.7, and 24.5.
5. The crystalline form of tromethamine salt of valproic acid of Claim 2 characterized by an X-ray diffraction pattern having characteristic peaks expressed in degrees 2θ (± 0.2°) at 5.4, 6.4, 6.8, 7.3, 8.1, 8.7, 24.5, 27.0, and 29.4.
6. The crystalline form of tromethamine salt of valproic acid of Claim 2 characterized by a thermal analysis result indicative of a melting point range of about 55°C to about 60°C.
7. The crystalline form of tromethamine salt of valproic acid of Claim 6, wherein the thermal analysis result is a differential scanning calorimetry thermogram taken at a heating rate of 10°C/min, in a closed pan that exhibits a melting endotherm with a maximum at about 55°C to about 60°C.
8. The crystalline form of tromethamine salt of valproic acid of claim 7 wherein the melting endotherm has a magnitude of about 130 J/g.
9. The crystalline form of tromethamine salt of valproic acid of Claim 2 characterized by an infrared absorption spectrum containing peaks at 1059, 1535, and 1566 cm⁻¹.
10. The crystalline form of tromethamine salt of valproic acid of Claim 2, wherein said form provides an X-ray powder diffraction pattern substantially in accordance with FIG. 1.
11. The crystalline form of tromethamine salt of valproic acid of claim 2, wherein said form provides an X-ray powder diffraction pattern substantially in accordance with Table 1:

<table>
<thead>
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<tr>
<td>15.8</td>
<td>5.64</td>
</tr>
<tr>
<td>17.1</td>
<td>5.22</td>
</tr>
</tbody>
</table>
12. The crystalline form of tromethamine salt of valproic acid of claim 2, wherein said form provides a differential scanning calorimetry thermogram substantially in accordance with FIG. 2.

13. The crystalline form of claim 2, wherein said form provides an infrared spectrum substantially in accordance with FIG. 3.

14. A method of making a tromethamine salt of valproic acid, the method comprising:
   dissolving the valproic acid in at least one solvent;
   adding the tromethamine to the at least one solvent to form a reaction mixture; and
   allowing the valproic acid and tromethamine to react to form the tromethamine salt of
   valproic acid.

15. The process of Claim 14 further including evaporating the at least one solvent after the
   tromethamine salt of valproic acid is formed.

16. The process of Claim 14 wherein the valproic acid and tromethamine are in
   substantially equimolar amounts.

17. The method of Claim 14 wherein the at least one solvent is at least one
   pharmaceutically acceptable non-reactive solvent into which the valproic acid substantially dissolves.

18. The method of Claim 17 wherein the at least one solvent is selected from the group
   consisting of methanol, ethanol, propanol and mixtures thereof.

19. The method of Claim 14, wherein the step of allowing the valproic acid and
   tromethamine to react comprises:
   stirring the reaction mixture until the valproic acid and the tromethamine react to form
   tromethamine valproate; and
   removing the at least one solvent to yield the tromethamine valproate.

20. A pharmaceutical dosage form comprising tromethamine salt of valproic acid and a
    pharmaceutically acceptable carrier.

21. A pharmaceutical dosage form comprising a crystalline form of tromethamine salt of
    valproic acid and a pharmaceutically acceptable carrier.

22. The dosage form of Claim 21 wherein the crystalline form of tromethamine salt of
    valproic acid is characterized by at least one of:
    (i) an x-ray diffraction pattern having characteristic peaks expressed in degrees 2θ (± 0.2°) at
    5.4, 6.4, 6.8, 8.1, and 24.5;
and

(iii) an infrared absorption spectrum containing peaks at 1059, 1535, and 1586 cm\(^{-1}\).

23. The dosage form of Claim 21 wherein the dosage form is a solid dosage form.

24. A method of treating a patient, the method comprising administering an effective amount of a crystalline composition of tromethamine salt of valproic acid characterized by at least one of:

   (i) an x-ray diffraction pattern having characteristic peaks expressed in degrees 2\(\theta\) (± 0.2°) at 5.4, 6.4, 6.8, 8.1, and 24.5;

   (ii) a thermal analysis result indicative of a melting point range of about 55°C to about 60°C;

   and

   (iii) an infrared absorption spectrum containing peaks at 1059, 1535, and 1586 cm\(^{-1}\).

25. The method of Claim 23 wherein the patient is being treated for epileptic seizures, convulsions or bipolar disorder.
Figure 1.

Scattering Angle (degrees 2θ)
Figure 2.

Temperature (°C)
Figure 3.

Energy (cm$^{-1}$)
### INTERNATIONAL SEARCH REPORT

**International application No**

PCT/US2006/023106

### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C53/128 C07C211/03 C07C311/63 A61K31/19 A61P25/08

### B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

C07C A61K A61P

**Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched**

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO–Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>US 5 212 326 A (MEADE EDWIN M [CA]) 18 May 1993 (1993-05-18) column 1; claims 1-5; examples 1,2</td>
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<td>US 4 988 731 A (MEADE EDWIN M [CA]) 29 January 1991 (1991-01-29) column 1; claims 1,2; examples 1-3</td>
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* Special categories of cited documents:

* document defining the general state of the art which is not considered to be of particular relevance

*E* earlier document but published on or after the International filing date

*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

*O* document referring to an oral disclosure, use, exhibition or other means

*P* document published prior to the International filing date but later than the priority date claimed

**A** document defining the general state of the art which is not considered to be of particular relevance

**E** earlier document but published on or after the International filing date

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**O** document referring to an oral disclosure, use, exhibition or other means

**P** document published prior to the International filing date but later than the priority date claimed

* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is cited alone

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

* document member of the same patent family

**Date of the actual completion of the international search**

14 November 2006

**Date of mailing of the international search report**

24/11/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL--2280 HJ Rijswijk
Tel. (+31–70) 946–6040, Tx. 31 651 490 nl,
Fax. (+31–70) 340–3016

Authorized officer

van Laren, Martijn
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 24 and 25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III  Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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

1. [ ] All required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] All searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: 

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (3)) (January 2004)
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