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MICHAEL W. DOBBINS
CLERK, U.S. DISTRICT COURT

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

ABBOTT LABORATORIES, an Illinois corporation,

Plaintiff,

v.

MYLAN PHARMACEUTICALS INC., a West Virginia corporation,

Defendant.

06CV2201
JUDGE LEFKOW
MAGISTRATE VALDEZ

Judge

COMPLAINT

Plaintiff Abbott Laboratories ("Abbott"), for its complaint against defendant Mylan Pharmaceuticals Inc. ("Mylan"), alleges as follows:

PARTIES

1. Abbott is a corporation organized under the laws of the State of Illinois, having its headquarters and principal place of business at Abbott Park, Illinois, 60064.

2. Mylan is a corporation organized under the laws of the State of West Virginia, having its headquarters at 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, West Virginia, 26504-4310.

JURISDICTION AND VENUE

3. This Court has jurisdiction over this suit pursuant to 28 U.S.C. § 1331 and § 1338(a), as it arises under an Act of Congress relating to patents, Title 35, United States Code, § 1, *et seq.* Specifically, this action arises under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2).

4. Mylan is subject to personal jurisdiction in Illinois. *See Abbott Laboratories v. Mylan Pharmaceuticals Inc.*, Slip Op., 2006 WL 850916 (N.D. Ill. Mar. 28, 2006) (Kendall, J.).

5. Venue properly exists in this judicial district pursuant to 28 U.S.C. § 1391 and § 1400(b).

FACTUAL BACKGROUND

The '731 and '326 Patents

6. The United States Food and Drug Administration ("FDA") approved Abbott's New Drug Application No. 21168 to market DEPAKOTE® (divalproex sodium) Extended Release ("ER") in a 500 mg dosage strength on August 4, 2000. DEPAKOTE® (divalproex sodium) ER was subsequently approved by FDA in a 250 mg dosage strength on May 31, 2002. As a result, DEPAKOTE® (divalproex sodium) ER is included on the FDA's list of "Approved Drug Products With Therapeutic Equivalence Evaluations," also known as the "Orange Book." Approved drugs may be used as the basis of a later applicant's Abbreviated New Drug Application ("ANDA") to obtain approval of the ANDA applicant's generic drug product under the provisions of 21 U.S.C. § 355(j).

7. United States Patent No. 4,988,731 ("the '731 patent"), titled Sodium Hydrogen Divalproate Oligomer, issued on January 29, 1991. (A copy of the '731 patent is attached as Exhibit A.) The '731 patent expires January 29, 2008.

8. United States Patent No. 5,212,326 ("the '326 patent"), also titled Sodium Hydrogen Divalproate Oligomer, issued on May 13, 1993. (A copy of the '326 patent is attached as Exhibit B.) The '326 patent expires January 29, 2008.

9. Abbott is the owner of the '731 and '326 patents.

10. The claims of the '731 and '326 patents have been interpreted by the United States Court of Appeals for the Federal Circuit, which has ruled that theses patents are valid and enforceable and that they cover divalproex sodium. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367 (Fed. Cir. 2002); *see also Abbott Labs. v. TorPharm, Inc.*, 156 F. Supp. 2d 738 (N.D.

Ill. 2001) (Norgle, J.); *Abbott Labs. v. TorPharm, Inc.*, 309 F. Supp. 2d 1043 (N.D. Ill. 2004) (Posner, J., sitting by designation); *Abbott Labs. v. Alra Labs.*, 1997 WL 667796 (N.D. Ill. 1997) (Zagel, J.).

11. The '731 and '326 patents are listed in the "Orange Book" in association with DEPAKOTE® (divalproex sodium) ER.

Mylan Notifies Abbott Regarding the Filing of ANDA 77-567

12. Abbott received a letter from Mylan's counsel, dated April 12, 2005, stating that Mylan had filed ANDA 77-567 requesting FDA approval to market "Divalproex Sodium Extended release Tablets, 500 mg."

13. In the April 12, 2005 letter, Mylan did not challenge the validity or enforceability of the '731 and '326 patents, did not deny that its proposed product would infringe the '731 and '326 patents, and indicated that it was only seeking FDA approval to market its proposed product after the '731 and '326 patents had expired.

14. Nearly six months later, Abbott received a second letter from Mylan regarding ANDA 77-567, this one dated October 5, 2005.

15. In the October 5, 2005 letter, Mylan indicated that it had switched course with respect to the '731 and '326 patents. In particular, Mylan stated that it had amended ANDA 77-567 to include a so-called Paragraph IV Certification as to those patents, meaning that Mylan was now asserting that its proposed divalproex sodium product should be approved by the FDA for marketing prior to the expiration of Abbott's '731 and '326 patents, because, in Mylan's view, those patents were either invalid, unenforceable, or would not be infringed by Mylan's product. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

16. Mylan attached to its October 5, 2005 letter a purportedly "detailed statement of the legal and factual basis" for the Paragraph IV Certification with regards to the '731 and '326 patents. Critically, this statement did not include any explanation as to why Mylan's proposed product would not infringe the '731 and '326 patents. If Mylan were going to claim non-infringement, it was required to provide such an explanation to Abbott as part of that letter. *See* 21 U.S.C § 355(j)(2)(B)(iv); *see also* 21 C.F.R. § 314.95(c)(6)(i) - (ii). Mylan's statement purporting to reserve further argument on this point is plainly insufficient under the Hatch-Waxman Act to preserve any claim of non-infringement. *Id.*

17. On March 22, 2006, Mylan sent another letter to Abbott relating to ANDA No. 77-567. This letter indicated that Mylan had amended ANDA No. 77-567 to add a request to market its proposed generic divalproex sodium product in a 250 mg. dosage strength.

18. Mylan attached to its March 22, 2006 letter a purportedly "detailed factual and legal basis" for the Paragraph IV Certification with regards to the '731 and '326 patents. Critically, this statement did not include any explanation as to why Mylan's proposed product would not infringe the '731 and '326 patents, other than to suggest (contrary to controlling Federal Circuit precedent) that those patents are invalid. If Mylan were going to claim non-infringement, it was required to provide such an explanation to Abbott as part of that letter. *See* 21 U.S.C § 355(j)(2)(B)(iv); *see also* 21 C.F.R. § 314.95(c)(6)(i) - (ii). Mylan's statement purporting to reserve further argument on this point is plainly insufficient under the Hatch-Waxman Act to preserve any claim of non-infringement. *Id.*

19. In addition, in its April 12, 2005, October 5, 2005, and March 22, 2006 letters, Mylan averred that the active ingredient in its proposed product is "Divalproex Sodium," which is the active ingredient in Abbott's DEPAKOTE® and is covered by one or more of the claims of

the '731 and '326 patents. Pursuant to the Hatch-Waxman Act and the implementing regulations from FDA, the fundamental requirement for filing an ANDA is that the active ingredient in the ANDA applicant's proposed product be "the same" as the active ingredient in the branded drug, in this case, DEPAKOTE®. *See* 21 U.S.C. § 355(j)(2)(A)(ii)(I) (an ANDA shall contain "information to show that the active ingredient of the new drug is the same as that of the listed drug"); 21 C.F.R. § 314.92 ("[f]or determining the suitability of an abbreviated new drug application, the term 'same as' means identical in active ingredient(s) . . . ."); 54 FR 28872, 28881 (July 10, 1988) ("The agency interprets the requirement that the active ingredients in the proposed product be the same as those of the listed drug to mean that the active ingredients must be identical. For example, if the proposed drug product contained a different salt or ester of the active ingredient in the listed drug, the active ingredient would not be identical to the active ingredient in the listed drug, and could not, therefore be approved in an ANDA. Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.").

COUNT I

INFRINGEMENT OF THE ' 731 PATENT

20. Abbott repeats and incorporates by reference each and every allegation of paragraphs 1-19 as if fully set forth herein.

21. Under 35 U.S.C. § 271(e)(2), the submission of an ANDA under 21 U.S.C. § 355(j) for a drug claimed in a patent or for a drug use claimed in a patent is an act of infringement if the applicant seeks FDA marketing approval effective prior to the expiration of the patent. Mylan's submission of ANDA 77-567 for approval to sell divalproex sodium extended-release tablets in 500 mg. and 250 mg. dosage strengths before the expiration of the '731 patent constitutes an act of infringement of that patent pursuant to 35 U.S.C. § 271(e)(2). In

addition, Mylan's generic version of DEPAKOTE® (divalproex sodium) ER in the 250 mg. and 500 mg. dosage strengths contains divalproex sodium and therefore infringes the '731 patent.

22. Abbott has no adequate remedy at law to redress Mylan's infringement.

COUNT II

INFRINGEMENT OF THE ' 326 PATENT

23. Abbott repeats and incorporates by reference each and every allegation of paragraphs 1-19 as if fully set forth herein.

24. Under 35 U.S.C. § 271(e)(2), the submission of an ANDA under 21 U.S.C. § 355(j) for a drug claimed in a patent or for a drug use claimed in a patent is an act of infringement if the applicant seeks FDA marketing approval effective prior to the expiration of the patent. Mylan's submission of ANDA 77-567 for approval to sell divalproex sodium extended-release tablets in 500 mg. and 250 mg. dosage strengths before the expiration of the '326 patent constitutes an act of infringement of that patent pursuant to 35 U.S.C. § 271(e)(2). In addition, Mylan's generic version of DEPAKOTE® (divalproex sodium) ER in the 250 mg. and 500 mg. dosage strengths contains divalproex sodium and therefore infringes the '326 patent.

25. Abbott has no adequate remedy at law to redress Mylan's infringement.

WHEREFORE, Abbott prays for the following relief:

(a) a judgment that the '731 patent is infringed under 35 U.S.C. § 271(e)(2) by the filing of ANDA 77-567;

(b) a judgment that the '326 patent is infringed under 35 U.S.C. § 271(e)(2) by the filing of ANDA 77-567;

(c) an order declaring that ANDA 77-567 cannot be approved earlier than the expiration date of Abbott's '731 patent;

(d) an order declaring that ANDA 77-567 cannot be approved earlier than the expiration date of Abbott's '326 patent;

(e) an injunction preventing Mylan, or any of its affiliates, from commercially manufacturing, selling, offering to sell, importing, or using divalproex sodium, or otherwise infringing one or more claims of the '731 patent during the life of the patent;

(f) an injunction preventing Mylan, or any of its affiliates, from commercially manufacturing, selling, offering to sell, importing, or using divalproex sodium, or otherwise infringing one or more claims of the '326 patent during the life of the patent;

(g) an award of Abbott's costs and attorneys' fees pursuant to 35 U.S.C. § 271(e)(4) and § 285; and

(h) such other and further relief as this Court may deem just and proper.

Dated: April 20, 2006

Respectfully submitted,

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Attorneys for Abbott Laboratories

Exhibit A

United States Patent [19]

Meade

[11] **Patent Number: 4,988,731**

[45] **Date of Patent: Jan. 29, 1991**

[54] **SODIUM HYDROGEN DIVALPROATE OLIGOMER**

[75] Inventor: **Edwin M. Meade**, Duncan, Canada

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[21] Appl. No.: **117,945**

[22] Filed: **Nov. 9, 1987**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 68,284, Aug. 20, 1979, abandoned.

[51] **Int. Cl.**^{5} **A61K 31/00; C07C 53/128**

[52] **U.S. Cl.** **514/557**; 562/606

[58] **Field of Search** 562/606; 514/557

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,895,976	7/1959	Kairys et al.	260/419
2,915,537	12/1959	Meade	260/419
4,127,604	11/1978	Chignac et al.	562/606
4,558,070	12/1985	Bauer et al.	514/557

FOREIGN PATENT DOCUMENTS

1074978	10/1954	France	562/606
2442M	4/1964	France	562/606

OTHER PUBLICATIONS

"The Pharmacological Studies on Sodium Dipropylacetate Anticonvulsant Activities and General Pharmalogical Actions", K. Shuto and T. Nishigaki, Applied Pharmacology, 4[6], pp. 937-949 (1970).

Primary Examiner—Vivian Garner
Attorney, Agent, or Firm—Steven F. Weinstock

[57] **ABSTRACT**

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

2 Claims, No Drawings

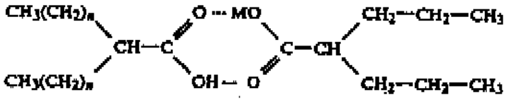
SODIUM HYDROGEN DIVALPROATE OLIGOMER

This is a continuation-in-part of copending application Serial No. 68,284, filed Aug. 20, 1979 now abandoned.

This invention relates to salts of valproic acid. In the last decade, 2-propylpentanoic acid and its alkali or earth alkali salts (hereinafter referred to as valproic acid and valproates or valproate salts, respectively) have been introduced in the arsenal of drugs useful for treating epileptic seizures or convulsions. Most commonly used are valproic acid itself or its sodium salt. The former is a liquid and as such is less desirable for preparing an oral dosage form while the latter is a solid that has poor stability characteristics partially due to pronounced hygroseopicity.

It has now been found that a highly stable, nonhygroscopic, solid entity can be prepared from valproic acid and its salts, representing a single chemical molecule with welldefined physical characteristics.

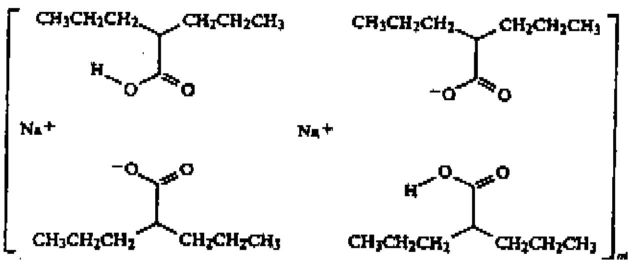
The new compound represents a single crystalline entity consisting of one molecule each of valproic acid or diethylacetic and a sodium valproate salt. There has been some uncertainty as to the structure of the compound. It was first hypothesized that the compound formed a complex in the form of a compound thus:



(I)

where M represented Na and n is 1 or 2.

Subsequent investigations have confirmed that the compound consists of one molecule each of valproic acid or diethylacetic acid and sodium valproate. However, it has been found that the molecules are distributed as an ionic oligomer, rather than as a dimer as originally believed. Thus, the sodium salt may be illustrated:



(II)

wherein m is about 2.

As can be seen from the foregoing structure, one mole each of the valproic acid moieties form coordinate bonds with the sodium of the sodium valproate molecule, and the valproate ion is ionically bonded to the sodium atom. The structure is thus consistent with the unique characteristics of the compound.

In the simplest embodiment, the above compound is prepared by dissolving one mole each of $[Me(CH_2)_n]_2$—CHCOOH and sodium valproate in 1000 ml of acetone at about 50° C. After cooling the solution to 0° C. or below, the formed new compound is filtered, washed if desired with pre-cooled acetone, and dried under reduced pressure to remove all traces of acetone. Alternately, the new compound wherein n=2 can be made in a two-component liquid medium which includes acetone. In this instance, sodium valproate is formed in situ by adding NaOH at a level of one half of a molecular equivalent of the valproic acid present, preferably as a solution in an acetone-miscible solvent for said NaOH, e.q. water. The new compound can be recovered from the liquid phase by evaporating the solvent(s) and, if desired, the new compound can be recrystallized, for instance from acetone/water, from acetonitrile or others, or the material may be spray-dried, lyophilized or purified by chromatography.

The new compound represents a single chemical molecule as can be determined by microanalysis, nmr spectrum, mixed melting point determination, IR spectrum and/or X-ray diffraction. The new compound does not have the aforementioned detrimental physical characteristics of either of the two starting materials; it is a crystalline, stable solid. Surprisingly, such a useful compound can be made only from valproic acid and diethylacetic acid on one side of the molecule, with the sodium or salt of valproic acid. When other valproate salts are used, i.e., the potassium, ammonium or magnesium salts, the resulting compound, either does not crystallize, does not form or is highly unstable in the presence of any atmospheric moisture.

The process for making the compounds of this invention are best illustrated by reference to the following examples which, however, are not intended to limit the invention in any respect.

EXAMPLE 1

In 1000 ml of acetone at about 50° C. is dissolved 166 g of sodium valproate and 144 g of valproic acid. The solution is cooled to about 0° C., filtered and the crystalline precipitate is washed with pre-cooled acetone at about 0° C. The new compound is obtained in a yield of 90% of theory. Additional material can be obtained by using the acetone filtrate in a subsequent batch.

The new material is a stable, white, crystalline powder which melts at 98–100° C. Its moisture stability is established by placing samples of the material for 45 minutes in a controlled environment at room temperature and 80% relative humidity. No weight gain is observed, while under the same condition, the simple sodium salt of valproic acid gains between 17 and 24% in weight.

The infrared spectrum is consistent with proposed structure II and has the following characterizing absorption bands: strong bands at 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}. The first two of these indicate the various methyl groups, the last two are due respectively to the antisymmetric and symmetric O—C—O—stretching vibrations of the carboxyl salt. The remaining strong bands indicate the stretching vibrations of the various methylene groups and the C=O in the carboxylic acid group, while the weak, broad bands at 2450 and 1900 cm^{-1} are due to intramolecularly bounded OH groups of the carboxylic acid.

EXAMPLE 2

In the fashion of Example 1 but using sodium valproate with the molar equivalents of dibutylacetic acid or diethylacetic acid, respectively, the corresponding hydrogen sodium mixed salts of the assumed structure II with n=b 3 or 1, respectively, are obtained. In the instance of dibutylacetic acid, a very hygroscopic product is obtained which is very difficult to handle and therefore unsuitable for pharmaceutical dosage forms. The mixed salt obtained with diethylacetic acid is a white crystalline powder which is stable to ordinary storage conditions and essentially nonhygroscopic.

EXAMPLE 3

In a comparison of anticonvulsant activities of
A: valproic acid (stable, liquid)
B: sodium valproate (hygroscopic solid)
C: compound (stable solid) of Example 1
the oral ED50 based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

	A	B	C
Audiogenic seizures (mice)	154	141	81 mg/kg
Pentylenetetrazole seizures (mice)	<800	282	178 mg/kg
Pentylenetetrazole seizures (rats)	355	415	362 mg/kg

In a bioavailability study carried out with (A) and (C) above in various animal species, the peak blood plasma levels of oral, equimolar doses are determined according to standard procedures, 30 minutes after drug administration.

	A	C
Mouse (200 mg/kg)	133.7	207.4 mg/kg
Rat (200 mg/kg)	84.1	63.0 mg/kg
Dog (25 mg/kg)	65.2	73.6 mg/kg
Dog (25 mg/kg) AUC*	82.3	95.0 hr · mcg/ml

*Area under the curve value for 0-7 hours.

From the above examples, it will be seen that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either "monomer" from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms, and specific amounts can be weighed out and blended with starch and/or other binders to form a flowable powder which can be forwarded to standard tableting machines after granulation. Neither the hygroscopic sodium salt of valproic acid nor the liquid valproic acid itself can be processed in this fashion without special precautions or absorbents.

The new compounds can be tableted in accordance with Example XIII of U.S. Pat. No. 3,325,361 and analogous methods. In these procedures, one or more diluents and/or excipients are used, e.g., starch, talcum powder, lubricants, disintegrators, flavoring agents, coloring agents and the like. These additives, of course, are the usual pharmaceutically acceptable carriers or diluents employed in routine fashion by tablet formulators.

The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(CH_3CH_2CH_2)_2CHCO_2Na/R_2CHCO_2H$ or $[(R_2CHCO_2)(R_2CHCO_2)]Na,H$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims.

I claim:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 such units.

* * * * *

Exhibit B

US005212326A

United States Patent [19]

Meade

[11] **Patent Number: 5,212,326**

[45] **Date of Patent: * May 18, 1993**

[54] **SODIUM HYDROGEN DIVALPROATE OLIGOMER**

[75] Inventor: **Edwin M. Meade**, Duncan, Canada

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[*] Notice: The portion of the term of this patent subsequent to Jan. 29, 2008 has been disclaimed.

[21] Appl. No.: **637,828**

[22] Filed: **Jan. 7, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 117,945, Nov. 9, 1987, Pat. No. 4,988,731, which is a continuation of Ser. No. 545,719, Oct. 26, 1983, abandoned, which is a continuation-in-part of Ser. No. 68,284, Aug. 20, 1979, abandoned.

[51] **Int. Cl.**^{5} C07B 53/00; A01N 37/00; A61K 31/19

[52] **U.S. Cl.** 562/606

[58] **Field of Search** 562/606; 514/557

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,127,604	11/1978	Chignac et al.	562/606
4,558,070	12/1985	Bauer et al.	562/606 X
4,988,731	1/1991	Meade	562/606 X

FOREIGN PATENT DOCUMENTS

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2442M	4/1964	France	562/606

Primary Examiner—José G. Dees
Assistant Examiner—Joseph M. Conrad
Attorney, Agent, or Firm—Steven F. Weinstock

[57] **ABSTRACT**

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

5 Claims, No Drawings

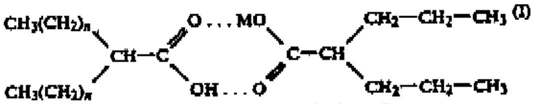
SODIUM HYDROGEN DIVALPROATE OLIGOMER

This application is a continuation of Ser. No. 117,945, filed Nov. 9, 1987, now U.S. Pat. No. 4,988,731 issued Jan. 29, 1991, which is a continuation of Ser. No. 545,719 filed Oct. 26, 1983, now abandoned, which is a continuation-in-part of Ser. No. 068,284 filed Aug. 20, 1979, now abandoned.

This invention relates to salts of valproic acid. In the last decade, 2-propylpentanoic acid and its alkali or earth alkali salts (hereinafter referred to as valproic acid and valproates or valproate salts, respectively) have been introduced in the arsenal of drugs useful for treating epileptic seizures or convulsions. Most commonly used are valproic acid itself or its sodium salt. The former is a liquid and as such is less desirable for preparing an oral dosage from while the latter is a solid that has poor stability characteristics partially due to pronounced hygroscopicity.

It has now been found that a highly stable, nonhygroscopic, solid entity can be prepared from valproic acid and its salts, representing a single chemical molecule with welldefined physical characteristics.

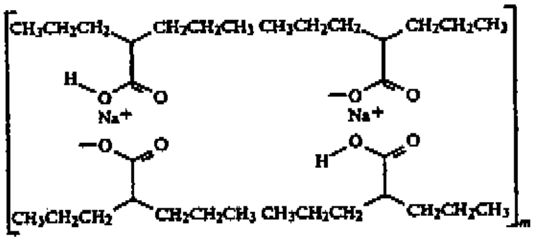
The new compound represents a single crystalline entity consisting of one molecule each of valproic acid or diethylacetic and a sodium valproate salt. There has been some uncertainty as to the structure of the compound. It was first hypothesized that the compound formed a complex in the form of a compound thus:



(I)

where M represented Na and n is 1 or 2.

Subsequent investigations have confirmed that the compound consists of one molecule each of valproic acid or diethylacetic acid and sodium valproate. However, it has been found that the molecules are distributed as an ionic oligomer, rather than as a dimer as originally believed. Thus, the sodium salt may be illustrated:



wherein m is about 2 to 3.

As can be seen from the foregoing structure, one mole each of the valproic acid moieties form coordinate bonds with the sodium of the sodium valproate molecule, and the valproate ion is ionically bonded to the sodium atom. The structure is thus consistent with the unique characteristics of the compound.

In the simplest embodiment, the above compound is prepared by dissolving one mole each of $[Me(CH_2)_n]_2CHCOOH$ and sodium valproate in 1000 ml of acetone at about 50° C. After cooling the solution to 0° C. or below, the formed new compound is filtered, washed if desired with pre-cooled acetone, and dried under reduced pressure to remove all traces of acetone. Alternately, the new compound wherein n=2 can be made in a two-component liquid medium which includes acetone. In this instance, sodium valproate is formed in situ by adding NaOH at a level of one half of a molecular equivalent of the valproic acid present, preferably as a solution in an acetone-miscible solvent for said NaOH, e.g. water. The new compound can be recovered from the liquid phase by evaporating the solvent(s) and, if desired, the new compound can be recrystallized, for instance from acetone/water, from acetonitrile or others, or the material may be spray-dried, lyophilized or purified by chromatography.

The new compound represents a single chemical molecule as can be determined by microanalysis, nmr spectrum, mixed melting point determination, IR spectrum and/or X-ray diffraction. The new compound does not have the aforementioned detrimental physical characteristics of either of the two starting materials; it is a crystalline, stable solid. Surprisingly, such a useful compound can be made only from valproic acid and diethylacetic acid on one side of the molecule, with the sodium or salt of valproic acid. When other valproate salts are used, i.e., the potassium, ammonium or magnesium salts, the resulting compound, either does not crystallize, does not form or is highly unstable in the presence of any atmospheric moisture.

The process for making the compounds of this invention are best illustrated by reference to the following examples which, however, are not intended to limit the invention in any respect.

EXAMPLE 1

In 1000 ml of acetone at about 50° C. is dissolved 166 g of sodium valproate and 144 g of valproic acid. The solution is cooled to about 0° C., filtered and the crystalline precipitate is washed with pre-cooled acetone at about 0° C. The new compound is obtained in a yield of 90% of theory. Additional material can be obtained by using the acetone filtrate in a subsequent batch.

The new material is a stable, white, crystalline powder which melts at 98°-100° C. Its moisture stability is established by placing samples of the material for 45 minutes in a controlled environment at room temperature and 80% relative humidity. No weight gain is observed, while under the same condition, the simple sodium salt of valproic acid gains between 17 and 24% in weight.

The infrared spectrum is consistent with proposed structure II and has the following characterizing absorption bands: strong bands at 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}. The first two of these indicate the various methyl groups, the last two are due respectively to the antisymmetric and symmetric O-C-O-stretching vibraitons of the carboxyl salt. The remaining strong bands indicate the stretching vibrations of the various methylene groups and the C=O in the carboxylic acid group, while the weak, broad bands at 2450 and 1900 cm^{-1} are due to intramolecularly bounded OH groups of the carboxylix acid.

EXAMPLE 2

In a comparison of anticonvulsant activities of

A: valproic acid (stable, liquid)
B: sodium valproate (hygroscopic solid)
C: compound (stable solid) of Example 1

the oral ED50 based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

	A	B	C
Audiogenic seizures (mice)	154	141	81 mg/kg
Pentylenetetrazole seizures (mice)	<800	282	178 mg/kg
Pentylenetetrazole seizures (rats)	355	415	362 mg/kg

In a bioavailability study carried out with (A) and (C) above in various animal species, the peak blood plasma levels of oral, equimolar doses are determined according to standard procedures, 30 minutes after drug administration.

	A	C
Mouse (200 mg/kg)	133.7	207.4 mg/kg
Rat (200 mg/kg)	84.1	63.0 mg/kg
Dog (25 mg/kg)	65.2	73.6 mg/kg
Dog (25 mg/kg) AUC*	82.3	95.0 hr · mcg/ml

*Area under the curve value for 0–7 hours.

From the above examples, it will be seen that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either "monomer" from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms, and specific amounts can be weighed out and blended with starch and/or other binders to form a flowable powder which can be forwarded to standard tableting machines after granulation. Neither the hygroscopic sodium salt of valproic acid nor the liquid valproic acid itself can be processed in this fashion without special precautions or absorbents.

The new compounds can be tableted in accordance with Example XIII of U.S. Pat. No. 3,325,361 and analogous methods. In these procedures, one or more diluents and/or excipients are used, e.g., starch, talcum powder, lubricants, disintegrators, flavoring agents, coloring agents and the like. These additives, of course, are the usual pharmaceutically acceptable carriers or diluents employed in routine fashion by tablet formulators.

The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(CH_3CH_2CH_2)_2CHCO_2Na/R_2CHCO_2H$ or $[(R_2CHCO_2)(R_2CHCO_2)]Na,H$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims.

I claim:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 to 6 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 4 to 6 such units.

3. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 6 such units.

4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$, and having physical/chemical properties as follows:

a. stable, white crystalline powder;

b. melting point of 98°–100° C.; and

c. an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1}.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,212,326 Page 1 of 2
DATED : May 18, 1993
INVENTOR(S) : Edwin M. Meade

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 1

Line 19, replace "from" with --"form"--

Line 25, replace "welldefined" with --"well-defined"--

Add --"II"-- adjacent to structure located between lines 47-55

Column 2

Line 5, underline separately --"in situ"--
Line 57, replace "vibraitons" with --"vibrations"--
Line 61, replace "bounded" with --"bonded"--
Line 62, replace "carboxylix" with --"carboxylic"--

Column 4

Line 24, replace "unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$" with

--"unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$"--

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

Page 2 of 2

PATENT NO. : 5,212,326

DATED : May 18, 1993

INVENTOR(S) : Edwin M. Meade

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,

Line 35, replace "unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2$ $CHCO_2H$" with

--"unit formula, $(CH_3CH_2CH_2)_2CHCO_2Na/(CH_3CH_2CH_2)_2CHCO_2H$"--

Signed and Sealed this

Third Day of May, 1994

Attest:

Bruce Lehman

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks