IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Andrew T. Berry
William O'Shaughnessy
Nicole Corona
McCARTER & ENGLISH
Four Gateway Center
100 Mulberry St.
Newark, New Jersey 07102
Phone: (973) 622-4444
Facsimile: (973) 624-7070

Of Counsel:
Robert L. Baechtold
Henry J. Renk
Nicholas N. Kallas
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112
Phone: (212) 218-2100
Facsimile: (212) 218-2200

Attorneys for Plaintiffs
Novartis Pharmaceuticals Corporation,
Novartis Corporation and
Novartis AG

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS CORPORATION and NOVARTIS AG,	:	
Plaintiffs,	:	
v.	:	
ROXANE LABORATORIES, INC.,	:	Civil Action No. _____
Defendant.	:	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Novartis Pharmaceuticals Corporation, Novartis Corporation and Novartis AG (hereinafter "Plaintiffs"), for their Complaint against Defendant Roxane Laboratories, Inc. allege as follows:

NATURE OF ACTION

1. This is an action for patent infringement.

PARTIES

2. Plaintiff Novartis Pharmaceuticals Corporation ("NPC") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

3. Plaintiff Novartis Corporation is a corporation organized and existing under the laws of the State of New York, having a place of business at 180 Park Avenue, Florham Park, New Jersey 07932.

4. Plaintiff Novartis AG is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056, Basel, Switzerland.

5. On information and belief, defendant Roxane Laboratories, Inc. ("Roxane") is registered to do business in New Jersey, and the Corporation Trust Company, 820 Bear Tavern Road, West Trenton, New Jersey 08628, is its registered agent in New Jersey.

6. On information and belief, Roxane is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

JURISDICTION AND VENUE

7. This action arises under the patent laws of the United States of America.

This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

8. On information and belief, Roxane sells various products and does business throughout the United States, including within this District.

9. On information and belief, Roxane previously has submitted to the jurisdiction of the United States District Court for the District of New Jersey.

10. This Court has personal jurisdiction over Roxane by virtue of, *inter alia*, the facts alleged in paragraphs 5, 8 and 9.

11. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 (c) and 1400(b).

CLAIM FOR RELIEF - PATENT INFRINGEMENT

12. Plaintiff NPC holds an approved new drug application ("NDA") No. 21-014 for Trileptal® tablets (150, 300 and 600 mg), which tablets contain the active ingredient oxacarbazepine. Trileptal® tablets were approved by the United States Food and Drug Administration ("FDA") on January 14, 2000 for the treatment of partial seizures in adults and children with epilepsy.

13. Oxacarbazepine is described in chemical nomenclature as 10, 11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide. The same compound is also referred to as oxcarbazepine. The terms oxacarbazepine and oxcarbazepine are synonymous and interchangeable.

14. Novartis AG is the owner of United States Patent No. 7,037,525 ("the '525 patent"), which discloses and claims a method of treating seizures comprising administering a formulation of oxacarbazepine. The '525 patent was duly and legally issued on May 2, 2006.

A true copy of the '525 patent is attached hereto as Exhibit A.

15. Roxane submitted to the FDA an Abbreviated New Drug Application ("ANDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use or sale of generic oxacarbazepine tablets in dosage strengths of 150 mg, 300 mg and 600 mg (hereinafter referred to as "Roxane's Oxacarbazepine Tablets") before the expiration of the '525 patent.

16. By filing its ANDA under 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use or sale of Roxane's Oxacarbazepine Tablets before the expiration of the '525 patent, Roxane has committed an act of infringement under 35 U.S.C. § 271(e)(2)(A). Further, the commercial manufacture, use, offer for sale, sale and/or importation of Roxane's Oxacarbazepine Tablets will also infringe one or more claims of the '525 patent.

17. Each of Roxane's Oxacarbazepine Tablets, if approved by the FDA, will be used in a method of treating seizures, comprising oral administration of a formulation of oxacarbazepine, wherein said formulation comprises a therapeutically effective dose of oxacarbazepine and wherein said oxacarbazepine has a median particle size of approximately 2 μm to 12 μm. Such administration will constitute direct infringement of the '525 patent under 35 U.S.C. § 271(a).

18. Each of Roxane's Oxacarbazepine Tablets, if approved by the FDA, will be used in a method of treating seizures, which comprises administering a formulation of oxacarbazepine having improved bioavailability, wherein said oxacarbazepine consists essentially of oxacarbazepine having a maximum residue on a 40 μm sieve of less than or equal to 5%. Such administration will constitute direct infringement of the '525 patent under 35 U.S.C. § 271(a).

19. On information and belief, Roxane, with knowledge of the '525 patent, and knowing that such administration mentioned in paragraphs 17 and 18 above will directly infringe the '525 patent, and with the intent to cause the acts which constitute such direct infringement, will actively induce, encourage, aid and abet such acts, thus itself infringing the '525 patent under 35 U.S.C. § 271(b).

20. On information and belief, Roxane, with knowledge of the '525 patent, and knowing that such administration mentioned in paragraphs 17 and 18 above will directly infringe the '525 patent, will contribute to the infringement of the '525 patent under 35 U.S.C. § 271(c) by offering for sale and selling in the United States Roxane's Oxacarbazepine Tablets, which are a component and material part of the patented method, and not a staple article or commodity of commerce suitable for substantial non-infringing use. Roxane will conduct such activities knowing that Roxane's Oxacarbazepine Tablets are especially made and/or adapted for use in infringing the '525 patent. Patients using Roxane's Oxacarbazepine Tablets will infringe the '525 patent under 35 U.S.C. § 271(a).

21. Roxane made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification") that, in its opinion and to the best of its knowledge, the '525 patent is invalid.

22. In early May 2006, Roxane sent to Plaintiff NPC a notice, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B)(iv)(II) and the FDA regulations relating thereto, in which Roxane represented that it had filed an ANDA for its Oxacarbazepine Tablets, including its certification with respect to the '525 patent, and that it sought approval of its ANDA prior to the expiration of that patent.

23. In its notice letter, Roxane did not allege that the '525 patent was unenforceable. Roxane's notice letter alleged noninfringement of the '525 patent based only on its allegation that the '525 patent is invalid.

24. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of any approval of the aforementioned ANDA relating to Roxane's Oxacarbazepine Tablets be a date which is not earlier than February 12, 2018, the expiration date of the '525 patent, or any later date of exclusivity to which Plaintiffs are or become entitled.

25. Plaintiffs also are entitled to an award of damages for any commercial manufacture, use, offer for sale, sale and/or importation of Roxane's Oxacarbazepine Tablets, and any act committed by Roxane with respect to the subject matter claimed in the '525 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

26. On information and belief, when Roxane filed its ANDA, it was aware of the '525 patent and that the filing of its ANDA seeking approval prior to the expiration of the '525 patent was an act of infringement of this patent.

27. This is an exceptional case and Plaintiffs are entitled to an award of reasonable attorney fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. Judgment that Roxane has infringed one or more claims of the '525 patent by filing the aforesaid ANDA relating to Roxane's Oxacarbazepine Tablets;

B. A permanent injunction restraining and enjoining Roxane and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, sale within the United States, or importation into the United States, of drug products the use of which is claimed in the '525 patent;

C. An Order that the effective date of any approval of the aforementioned ANDA relating to Roxane's Oxcarbazepine Tablets be a date which is not earlier than the later of February 12, 2018, the expiration date of the '525 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. Damages from Roxane for any commercial activity constituting infringement of the '525 patent;

E. Judgment that this is an exceptional case and that Plaintiffs are entitled to their reasonable attorney fees pursuant to 35 U.S.C. § 285; and

F. Such other and further relief as the Court may deem just and proper.

Dated: August 30, 2006

Andrew T. Berry
William O'Shaughnessy
Nicole Corona
McCARTER & ENGLISH
Four Gateway Center
100 Mulberry St.
Newark, New Jersey 07102
Phone: (973) 622-4444
Facsimile: (973) 624-7070

Attorneys for Plaintiffs
Novartis Pharmaceuticals Corporation,
Novartis Corporation and
Novartis AG

Of Counsel:
Robert L. Baechtold
Henry J. Renk
Nicholas N. Kallas
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
Phone: (212) 218-2100
Facsimile: (212) 218-2200

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EXHIBIT A

US007037525B2

(12) **United States Patent**
Schlütermann

(10) **Patent No.: US 7,037,525 B2**
(45) **Date of Patent: May 2, 2006**

(54) **OXACARBAZEPINE FILM-COATED TABLETS**

(75) Inventor: **Burkhard Schlütermann**, Au (DE)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/429,634**

(22) Filed: **May 5, 2003**

(65) **Prior Publication Data**

US 2003/0190361 A1 Oct. 9, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/947,574, filed on Sep. 6, 2001, now abandoned, which is a continuation of application No. 09/367,361, filed as application No. PCT/EP98/00794 on Feb. 12, 1998.

(30) **Foreign Application Priority Data**

Feb. 14, 1997 (CH) 97/331

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 9/28 (2006.01)

(52) **U.S. Cl.** **424/474**; 424/475; 424/489; 424/465; 514/951

(58) **Field of Classification Search** 424/464, 424/465, 474, 475, 489, 479, 480, 490, 493, 424/494, 461, 463
See application file for complete search history.

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Primary Examiner—Thurman K. Page
Assistant Examiner—Pili A. Hawes
(74) *Attorney, Agent, or Firm*—Peter J. Waibel; E Jay Wilusz, Jr.

(57) **ABSTRACT**

The invention relates to formulations, e.g. film-coated tablets containing oxcarbazepine and to processes for the production of said formulations. The film-coated tablets have a tablet core comprising a therapeutically effective dose of oxacarbazepine being in a finely ground form having a mean particle size of from 4 to 12 μm (median value), and a hydrophilic permeable outer coating.

10 Claims, No Drawings

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OXACARBAZEPINE FILM-COATED TABLETS

This application is a continuation of application Ser. No. 09/947,574, filed Sep. 6, 2001 now abandoned, which is a continuation of application Ser. No. 09/367,361 filed on Aug. 11, 1999, which is a 371 of PCT/EP98/00794, filed Feb. 12, 1998, which in their entirety are herein incorporated by reference.

The present invention relates to formulations of oxcarbazepine, in particular film-coated tablets and to processes for the production of said formulations.

Oxcarbazepine, 10,11-dihydro-10-oxo-5H-dibenz[b,f] azepine-5-carboxamide, like ®Tegretol [(Novartis) carbamazepine: 5H-dibenz[b,f]azepine-5-carboxamide)], is an agent of first choice in the treatment of convulsions. The known dosage forms, such as tablets and liquid dosage forms, e.g.suspensions, are suitable for ensuring a uniform concentration of active ingredient in the blood, especially in the case of regularly recurring administration over a prolonged period of treatment. Nevertheless, it is always desirable to develop and improve upon existing formulations with respect to, for example bioavailability and compliance.

EP 0 646 374 discloses a formulation of oxacarbazepine which is coated with two layers (an inner and outer layer) containing pigments. The outer layer contains Iron Oxide. The double-coated tablet prevents inhomogeneous colouration of the formulation upon storage.

Despite the known forms of oxacarbazepine, it is always desirable to provide improved formulations.

We have now found formulations of oxacarbazepine which are easily processed into dosage forms and which may enhance the bioavailability of oxacarbazepine and increase compliance.

Accordingly, the invention provides in one of its aspects a formulation of oxacarbazepine comprising oxacarbazepine, preferably in a finely ground form, having a median particle size of approximately 2 to 12 μm, perferably 4 to 12 μm, more preferably 4 to 10 μm and with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%.

The formulation according to the invention may contain pharmaceutically acceptable excipients commonly used in pharmaceutical formulations, e.g. for oral administration.

In a preferred embodiment according to the invention the formulation may be in the form of a film-coated tablet which comprises,

a) a tablet core comprising a therapeutically effective dose of the oxacarbazepine, preferably in a finely ground form, having a median particle size of approximately from 2 to 12 μm, preferably 4 to 12 μm, more preferably 4 to 10 μm with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%, and further excipients that are suitable for the production of granules; and

b) a hydrophilic permeable outer coating.

The formulations, e.g. film-coated tablets according to the present invention use oxacarbazepine of fine particle size and narrow particle size distribution and as such may be formulated into dosage forms, e.g solid oral dosage forms such as tablets with relative ease. Furthermore, the fine particle size and narrow particle size distribution may also be beneficial in improving the bioavailablity of oxacarbazepine. Still further the formulations meet all customary requirements, such as storage stability and colour stability.

The colour stability may be achieved using only a single coating containing pigments rather than requiring a double coating containing pigments. This has the advantage of rendering the process of formulating the dosage forms relatively simple and efficient. Furthermore, for a given dosage size, e.g. 300 mg lower amounts of pigment, e.g. Iron oxide (when employed) are required in the coating.

The invention provides in another of its aspects a process for the production of a film-coated tablet containing oxacarbazepine comprising the steps of forming the oxacarbazepine, having a median particle size of approximately from, 2 to 12 μm, preferably 4 to 12 μm, more preferably 4 to 10 μm with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%, and optionally other excipients into a central core and coating said core with a hydrophilic permeable outer coating.

In a preferred aspect of the invention there is provided a process for the production of a film-coated tablet containing oxacarbazepine which comprises finely grinding oxacarbazepine to a median particle size of approximately from 2 to 12 μm, preferably 4 to 12 μm, more preferably 4 to 10 μm with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2% and, with the admixture of excipients that are suitable for granulation processes, forming the oxacarbazepine into granules, compressing the granules to form tablet cores using conventional tabletting processes, and providing the cores with a hydrophilic permeable outer coating.

Within the scope of the description of the invention, the terms used hereinbefore and hereinafter are defined as follows:

The term "film-coated tablet" denotes a perorally administrable, single-dose, solid dosage form that can be produced by compressing oxacarbazepine with conventional tabletting excipients to form a tablet core using conventional tabletting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating. Granulation methods are described, for example, in *Voigt, loc. cit.*, pages 156–169.

Suitable excipients for the production of granules are, for example pulverulent fillers optionally having flow-conditioning properties, for example talcum, silicon dioxide, for example synthetic amorphous anhydrous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, microcrystalline cellulose, for example of the Avicel® type (FMC Corp.), for example of the types AVICEL PH101, 102, 105, RC581 or RC 591, Emcocel® type (Mendell Corp.) or Elcema® type (Degussa); carbohydrates, such as sugars, sugar alcohols, starches or starch derivatives, for example lactose, dextrose, saccharose, glucose, sorbitol, mannitol, xylitol, potato starch, maize starch, rice starch, wheat starch or amylopectin, tricalcium phosphate, calcium hydrogen phosphate or magnesium trisilicate; binders, such as gelatin, tragacanth, agar, alginic acid, cellulose ethers, for example methylcellulose, carboxymethylcellulose or hydroxypropylmethylcellulose, polyethylene glycols or ethylene oxide homopolymers, especially having a degree of polymerisation of approximately from 2.0×10^3 to 1.0×10^5 and an approximate molecular weight of about from 1.0×10^5 to 5.0×10^6, for example excipients known by the name Polyox® (Union Carbide), polyvinylpyrrolidone or povidones, especially having a mean molecular weight of approximately 1000 and a degree of polymerisation of approximately from 500 to 2500, and also agar or gelatin; surface-active substances, for example anionic surfactants of the alkyl sulfate type, for example sodium, potassium or magnesium n-dodecyl sulfate, n-tetradecyl sulfate, n-hexadecyl sulfate or n-octadecyl sulfate, of the alkyl ether sulfate type, for example sodium, potassium or magnesium n-dodecyloxyethyl sulfate, n-tetradecyloxyethyl sulfate,

n-hexadecyloxyethyl sulfate or n-octadecyloxyethyl sulfate, or of the alkanesulfonate type, for example sodium, potassium or magnesium n-dodecanesulfonate, n-tetradecanesulfonate, n-hexadecanesulfonate or n-octadecanesulfonate, or non-ionic surfactants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000 stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronics® (BWC) or Synperonic® (ICI) type.

Granules may be produced in a manner known per se, for example using wet granulation methods known for the production of "built-up" granules or "broken-down" granules.

Methods for the formation of built-up granules may operate continuously and comprise, for example simultaneously spraying the granulation mass with granulation solution and drying, for example in a drum granulator, in pan granulators, on disc granulators, in a fluidised bed, by spray-drying or spray-solidifying, or operate discontinuously, for example in a fluidised bed, in a batch mixer or in a spray-drying drum.

Preferred are methods for the production of broken-down granules, which may be carried out discontinuously and in which the granulation mass first forms a wet aggregate with the granulation solution, which aggregate is then comminuted or formed into granules of the desired particle size and the granules then being dried. Suitable equipment for the granulation step are planetary mixers, low and high shear mixers, wet granulation equipment including extruders and spheronisers include, for example, apparatus from the companies Loedige, Glatt, Diosna, Fielder, Collette, Aeschbach, Alexanderwerk, Ytron, Wyss & Probst, Werner & Pfleiderer, HKD, Loser, Fuji, Nica, Caleva and Gabler.

The granulation mass consists of comminuted, preferably ground, oxacarbazepine and the excipients mentioned above, for example pulverulent fillers, such as microcrystalline cellulose of the AVICEL type. AVICEL PH 102 is especially suitable. Depending on the method used, the granulation mass may be in the form of a premix or may be obtained by mixing the oxacarbazepine into one or more excipients or mixing the excipients into the oxacarbazepine. The wet granules are preferably dried, for example in the described manner by tray drying or in a fluidised bed.

According to an alternative process variant, tablet cores are produced using the so-called compacting or dry granulation method in which the active ingredient is compressed with the excipients to form relatively large mouldings, for example slugs or ribbons, which are comminuted by grinding, and the ground material is compressed to form tablet cores.

Suitable excipients for the compacting method are preferably those which are suitable for the conventional direct compression methods, for example dry binders, such as starches, for example potato, wheat and maize starch, microcrystalline cellulose, for example commercial products available under the trademarks Avicel®, Filtrak®, Heweten® or Pharmacel®, highly dispersed silicon dioxide, for example Aerosil®, mannitol, lactose, and also polyethylene glycol, especially having a molecular weight of from 4000 to 6000, crosslinked polyvinylpyrrolidone (Polyplasdone® XL or Kollidon® CL), crosslinked carboxymethylcellulose (Acdisol® CMC-XL), carboxymethylcellulose [Nymcel®, for example ZSB-10, (Nyma)], hydroxypropylmethylcellulose, for example the quality HPMC 603, carboxymethyl starch [Explotab® (Mendell) or Primojel® (Scholtens)], microcrystalline cellulose, for example Avicel® PH 102, dicalcium phosphate, for example Emcompress® or talcum. The addition of small amounts of, for example, lubricants, such as magnesium stearate, is also advantageous.

Compression to form tablet cores may be carried out in conventional tabletting machines, for example EK-0 Korsch eccentric tabletting machines or rotary tabletting machines. The tablet cores may be of various shapes, for example round, oval, oblong, cylindrical etc., and various sizes, depending on the amount of oxacarbazepine.

Oxacarbazepine is known. Its manufacture and therapeutic use as an anticonvulsive are described in German Auslegeschrift 2 011 087 which is incorporated herein by reference. A commercially advantageous process for the preparation of that active ingredient is described in European Patent Application No. 0 028 028 which is incorporated herein by reference. Commercially available dosage forms are provided for peroral administration, for example tablets comprising 300 and 600 mg of active ingredient. Those dosage forms are known by the trademark ®Trileptal (Novartis) and have been introduced in a large number of countries, such as Denmark, Finland, Austria and Belgium.

The median particle size of the oxacarbazepine is approximately from 2 to 12 μm, preferably 4 to 12 μm, more preferably 4 to 10 μm with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%. In a preferred form of process, the median particle size of the oxacarbazepine is approximately from 4 to 12 μm, typically 6 to 8 μm with a maximum residue on a 40 μm sieve of up to 5%, e.g. 2%.

The known particle size analysis methods are suitable for determining the median particle size, for example particle size measurement using light, for example light-scattering methods or turbidimetric methods, sedimentation methods, for example pipette analysis using an Andreassen pipette, sedimentation scales, photosedimentometers or sedimentation in a centrifugal force field, pulse methods, for example using a Coulter counter, or sorting by means of gravitational or centrifugal force. Those methods are described, inter alia, in *Voigt, loc. cit.*, pages 64–79.

In order to produce oxacarbazepine particles, e.g. crystals having the desired particle size, conventional comminution and de-agglomeration techniques may be used, for example grinding in an air-jet mill or impact mill, a ball mill, vibration mill, mortar mill or pin mill.

The hydrophilic permeable outer coating b) comprises a film-forming material that is permeable to water and intestinal juice and that may be swellable, and is soluble or at least to some extent soluble, in those fluids.

Water-permeable film-forming materials are, for example, hydrophilic mixtures of polyvinylpyrrolidone or of a copolymer of polyvinylpyrrolidone and polyvinyl acetate with hydroxypropylmethylcellulose, mixtures of shellac with hydroxypropylmethylcellulose, polyvinyl acetate or copolymers thereof with polyvinylpyrrolidone, or mixtures of water-soluble cellulose derivatives, such as hydroxypropylmethylcellulose, and water-insoluble ethylcellulose.

The coating compositions may, if desired, be used in admixture with other additional excipients, such as talcum or silicon dioxide, for example synthetic amorphous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, or wetting agents, for example sorbates or plasticisers, for example the afore-mentioned polyethylene glycols.

Elastic, film-like materials are especially hydrophilic, partially etherified cellulose derivatives.

Hydrophilic, partially etherified cellulose derivatives are, for example, lower alkyl ethers of cellulose having an average degree of molar substitution (MS) that is higher than one and lower than three and an average degree of polymerisation of approximately from 100 to 5000.

The degree of substitution is a measure of the substitution of the hydroxy groups by lower alkoxy groups per glucose unit. The average degree of molar substitution (MS) is an averaged value and indicates the number of lower alkoxy groups per glucose unit in the polymer.

The average degree of polymerisation (DP) is also an averaged value and indicates the average number of glucose units in the cellulose polymer.

Lower alkyl ethers of cellulose are, for example, cellulose derivatives that are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit forming the cellulose chains and, where appropriate, at the second and third secondary hydroxy group by C_1–C_4alkyl groups, especially methyl or ethyl, or by substituted C_1–C_4alkyl groups, for example 2-hydroxyethyl, 3-hydroxy-n-propyl, carboxymethyl or 2-carboxyethyl.

Suitable lower alkyl ethers of cellulose are preferably cellulose derivatives that are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit by the mentioned C_1–C_4alkyl groups or by substituted C_1–C_4alkyl groups and at the second and, where appropriate, third secondary hydroxy group by methyl or ethyl groups. Suitable lower alkyl ethers of cellulose are especially methylcellulose, ethylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, ethylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose (in salt form, for example in sodium salt form) or methylcarboxymethylcellulose (also in salt form, for example sodium salt form).

Preferred lower alkyl ethers of cellulose are ethylcellulose (DP: approximately from 150 to 1000, MS: approximately from 1.2 to 1.8), for example of the Aquacoat® type (FMC Corp.), hydroxyethylcellulose (DP: approximately from 120 to 1200, MS: approximately from 1.2 to 2.5) and hydroxypropylcellulose (DP: approximately from 200 to 3000, MS: approximately from 1.0 to 3.0).

Water-permeable film-forming materials also include cellulose acetate trimellitate (CAT), and methacrylic acid/methacrylate 1:1 or 1:2 copolymer, for example EUDRAGIT L and S, for example EUDRAGIT L 12.5 or S 12.5.

The film-forming material may be sprayed on in the form of an aqueous dispersion of redispersible cellulose acetate phthalate—CAP—(Aquateric®: FMC), of polyvinyl acetate phthalate—PVAP—(Coateric®: Colorcon), of hydroxypropylmethylcellulose phthalate—HPMCP—(Aquacoat® HP 50 or HP 55: Shin-Etsu) or also, especially, of acrylic acid/methacrylic acid copolymer partially esterified by C_1–C_4alkyl groups.

Also suitable is an acrylic acid/methacrylic acid 1:1 copolymer partially esterified by methyl and/or ethyl groups of the type EUDRAGIT L 30 D or water-dispersed EUDRAGIT L 100-55.

The film-forming materials may comprise additional excipients, such as, for example, plasticisers, for example triethyl citrate, for example Citroflex® (Pfizer), triacetin, various phthalates, for example diethyl or dibutyl phthalate, mixed mono- or di-glycerides of the Myvacet® type (Eastman), for example MYVACET 9-40, the polyethylene glycols mentioned hereinbefore, for example having a molecular weight of approximately from 6000 to 8000, and also ethylene oxide/propylene oxide block copolymers of the Pluronic® (BASF) or Synperonic® (ICI) type, pulverulent mould release agents, for example magnesium trisilicate, starch or synthetic amorphous silicic acid of the SYLOID type, for example SYLOID 244 FP.

The hydrophilic permeable outer coating b) comprises white pigments, for example titanium dioxide pigments, preferably combined with iron oxide pigments. The iron oxide may be ferric or ferrous iron oxide, preferably Fe_2O_3 optionally in hydrated form. When iron oxide is employed, the amounts employed in the coating will depend upon the size of the particular dosage form. Preferably, the amount of iron oxide employed may be chosen from about 0.1 mg per dosage form, e.g. tablet, to 1.6 mg per dosage form, e.g. tablet, more preferably 0.3 mg per dosage form, e.g. tablet to 0.9 mg per dosage form, e.g. tablet.

The tablet cores may be coated with the hydrophilic permeable coating composition in a manner known per se, using conventional coating methods.

For example, the coating composition is dissolved or suspended in water in the desired quantity ratio. If desired, excipients, such as polyethylene glycol, are added. The solution or dispersion is sprayed onto the tablet cores together with other excipients, for example talcum or silicon dioxide, for example SYLOID 244 FP, for example using known methods, such as spray-coating in a fluidised bed, for example using the Aeromatic, Glatt, Wurster or Hüttlin (ball coater) system, or also in a coating-pan in accordance with the methods known by the names Accela Cota or immersion coating.

Preferably, an aqueous dispersion comprising hydroxypropylmethylcellulose (cellulose HPMC) and pigments is sprayed on.

The formulations, e.g. film-coated tablets according to the invention are useful for their anticonvulsive action and are useful as monotherapy or as adjunctive therapy in the control, prevention or treatment of seizure, e.g. resulting from the onset of epilepsy, status epilepticus, cerebrovascular disorders, head injury and alcohol withdrawal.

The exact dose of oxacarbazepine and the particular formulation to be administered depend upon a number of factors, e.g. the condition to be treated, the desired duration of treatment and the rate of release of the oxacarbazepine. For example, the amount of oxacarbazepine required and the release rate thereof may be determined by in vitro or in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

Preferred regimes include for monotherapy, 150 to 600 mg, e.g 300 mg twice per day. Doses of from 1200 to 2400 mg/day may be tolerated. Preferred regimes for adjunctive therapy include a starting dose of 300 mg/day. Doses from 600 to 2400 mg/day may be tolerated.

The following Examples illustrate the invention.

EXAMPLE 1

Example 1	Formulations (mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150	300	600
Avicel PH 102	32.8	65.6	131.2
Cellulose HPM 603	4.2	8.4	16.8
Polyvinylpyrrolidone	10	20	40
Aerosil 200	0.8	1.6	3.2
Magnesium stearate	2.2	4.4	8.8
	200	400	800
Coating:			
Polyethylene glycol (PEG) 8000	0.832	1.331	2.162
Cellulose HPM 603	4.595	7.352	11.947
Talcum	3.327	5.323	8.649
Titanium Dioxide	0.935	1.496	2.431
Iron oxide, yellow	0.312	0.499	0.81
	10	16	26
Total	210	416	826

Mix the TRILEPTAL, cellulose HPM 603 (binder) and AVICEL PH 102 (binder, filler, disintegration-promoting excipient) in a mixer, preferably in a high-speed mixer (DIOSNA, LOEDIGE, FIELDER, GLATT etc.). Add water as granulation liquid to the mixture, and knead in a mixer, preferably a high-speed mixer, until an adequate consistency is achieved. Alternatively, the binder cellulose HPM may be dissolved in the granulation liquid, water, beforehand. Granulate the wet granules using a suitable device (ALEXANDER Reibschnitzler, QUADRO-COMILL) and dry in a fluidised bed (AEROMATIC, GLATT). Add AVICEL PH 102, AEROSIL 200 (flow conditioner) and polyvinylpyrrolidone PXL (disintegrator) to the dry granules and comminute and mix in a comminuter (FREWITT, QUADRO-COMILL, FITZMILL). Finally, add magnesium stearate (lubricant) and mix (STOECKLIN container mixer, VRIECO mixer). Alternatively, the lubricant may be added directly to the comminuted material. Compress the final mixture to form TRILEPTAL tablets (eccentric press, rotary press: KILIAN, KORSCH, FETTE, MANESTY).

Coat the tablets with an aqueous preparation consisting of cellulose HPM 603 (film former), iron oxide yellow 17268 (pigment), PEG 8000 (plasticiser for the film former), talcum (anti-adhesive agent, covering agent) and titanium dioxide (covering agent) in a rotating coating pan (ACCELA-COTA, GLATT, DRIACOATER, DUMOULIN). Alternatively, it is possible to use, for example, fluidised-bed or air-suspension apparatus for the coating process (AEROMATIC, GLATT, FREUND, HUETTLIN).

EXAMPLE 2

	(mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150.0	300.0	600.0
Avicel PH 102	28.8	57.5	115.0
Cellulose HPM 603	5.0	10.0	20.0
Nymcel ZSB 10	13.8	27.5	55.0
Aerosil 200	1.3	2.5	5.0
Magnesium Stearate	2.3	4.5	9.0
Total:	201.0	402.0	804.0
Coating:			
Polyethylene glycol (PEG) 8000	0.915	1.497	2.328
Cellulose HPM 603	5.054	8.269	12.865
Talcum	3.659	5.988	9.314
Titanium dioxide	1.029	1.684	2.62
Iron oxide, yellow	0.343	0.561	0.873
	11	18	28
Total	212.0	420.0	832.0

The oxacarbazepine, cellulose HPM 603 and Avicel PH 102 are mixed together in a planetary mixer (Aeschbach). Alcohol is added to this mixture before it is kneaded in a planetary mixer until a desired consistency is achieved. Thereafter the methodology according to Example 1 is followed to provide coated tablets.

EXAMPLE 3

	(mg)	(mg)	(mg)
Tablet Core:			
Oxcarbazepine	150	300	600
Avicel PH 102	46	92	184
Cellulose HPM 603	6	12	24
Polyvinylpyrrolidone	10	20	40
Aerosil 200	0.8	1.6	3.2
Magnesium stearate	2.2	4.4	8.8
Total:	215	430	860
Coating:			
Polyethylene glycol (PEG) 8000	0.915	1.497	2.328
Cellulose HPM 603	5.054	8.269	12.865
Talcum	3.659	5.988	9.314
Titanium Dioxide	1.029	1.684	2.62
Iron oxide, yellow	0.343	0.561	0.873
	11	18	28
Total	226	448	888

The same methodology as Example 1 is carried out on the formulation to provide coated tablets.

What is claimed is:

1. A method of treating seizures, which comprises administering a formulation of oxacarbazepine having improved bioavailability, wherein said oxacarbazepine consists essentially of oxacarbazepine having a maximum residue on a 40 μm sieve of less than or equal to 5%.

2. The method according to claim 1 wherein said maximum residue on a 40 μm sieve is less than or equal to 5%.

3. The method according to claim 1 wherein said formulation is substantially free from particles greater than or equal to 40 μm in size.

4. The method according to claim 1 wherein the seizures results from the onset of epilepsy.

5. A method of treating seizures, comprising oral administration of a formulation of oxacarbazepine, wherein said formulation comprise a therapeutically effective dose of oxacarbazepine and wherein said oxacarbazepine has a median particle size of approximately 2 μm to 12 μm.

6. The method according to claim 5 wherein said oxacarbazepine has a median particle size of approximately 4 μm to 10 μm.

7. The method according to claim 5 wherein said oxacarbazepine has a median particle size of approximately 6 μm to 8 μm.

8. The method according to claim 5 wherein said oxacarbazepine has a maximum residue on a 40 μm sieve of less than or equal to 5%.

9. The method according to claim 5 wherein said oxacarbazepine has a maximum residue on a 40 μm sieve of less than or equal to 2%.

10. The method of claim 1, wherein said oxacarbazepine has a median particle sie of approximately 2 μm to 12 μm.

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