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

ORTHO-McNEIL)	
PHARMACEUTICAL, INC.,)	
)	
Plaintiff,)	
)	
v.)	
)	CIVIL ACTION NO. _____
BARR LABORATORIES, INC., and)	
BARR PHARMACEUTICALS, INC.,)	
)	
Defendants.)	
_____)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff, Ortho-McNeil Pharmaceutical, Inc. (“Ortho-McNeil”), by its undersigned attorneys, brings this action against defendants, Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc., for patent infringement and alleges as follows:

Parties

1. Plaintiff, Ortho-McNeil, is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1000 U.S. Route 202, Raritan, New Jersey 08869. Ortho-McNeil is engaged in the business of marketing prescription pharmaceutical products in the United States.

2. On information and belief, defendant Barr Laboratories, Inc. is a corporation having its principal place of business at 223 Quaker Road, Pomona, New York 10970.

3. On information and belief, defendant Barr Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, and having a principal place of business at 223 Quaker Road, Pomona, New York 10970.

4. On information and belief, defendant Barr Laboratories, Inc. is a subsidiary of defendant Barr Pharmaceuticals, Inc.

5. On information and belief, Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. are registered to do business in New Jersey. Further, on information and belief, Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. maintain executive offices and a manufacturing facility and otherwise transact business within this District.

6. On information and belief, the acts of Barr Laboratories, Inc. complained of herein, were done at the direction of, with the authorization of, or with the cooperation, participation, the assistance of or at least in part for the benefit of, Barr Pharmaceuticals, Inc.

7. Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. are referred to hereinafter, collectively, as “Barr.”

Jurisdiction and Venue

8. This action for patent infringement arises under the patent laws of the United States, Title 35, United States Code, Section 271(e)(2) and Title 21, United States Code, Section 355. Jurisdiction is based on Title 28, United States Code, Sections 1331 and 1338(a).

9. Venue is proper in this Court pursuant to Title 28, United States Code, Sections 1391(c) and 1400(b).

Ortho-McNeil's Patent

10. On October 24, 2006, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued United States Patent No. 7,125,560 (“the ‘560 patent,” a copy of which is attached as Exhibit A), entitled PHARMACEUTICAL COMPOSITION OF TOPIRAMATE, to Ortho-McNeil as assignee of the inventors Madhav S. Thakur, Pramod M. Kotwal and Irwin S. Gibbs. At all times subsequent to issuance of the ‘560 patent, Ortho-McNeil has been the owner of the entire right, title and interest in and to the ‘560 patent, including the right to sue and recover for infringement.

11. Ortho-McNeil is the holder of an approved New Drug Application (“NDA”) under Section 505(a) of the Federal Food Drug and Cosmetic Act (“FFDCA”), 21 U.S.C. § 355(a), for topiramate capsules (NDA 20-844), which are marketed in the United States under the trade name TOPAMAX[®]. The claims of the ‘560 patent cover methods of using pharmaceutical compositions containing the drug topiramate for treating convulsions in a mammal.

12. Pursuant to 21 U.S.C. § 355(b)(1), the ‘560 patent is identified in the Food and Drug Administration publication entitled “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”), as covering TOPAMAX[®] topiramate capsule products.

Barr's Actions

13. Pursuant to Section 505 of the FFDCA, Barr filed an Abbreviated New Drug Application (“ANDA”) for topiramate capsules, seeking approval to engage in the commercial manufacture, use, offer for sale and sale of topiramate capsules, 15 and 25 mg (“ANDA products”), before the ‘560 patent expires. The Barr ANDA number is 76-448.

14. In connection with the filing of its ANDA as described in the preceding paragraph, Barr has provided written certification to the Food and Drug Administration, as called for by § 505 of the FDCA, which certification alleges that the claims of the '560 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Barr's ANDA.

15. Barr sent written notice of its filing to Ortho-McNeil, which notice was received by Ortho-McNeil. The notice alleged that the claims of the '560 patent are invalid, unenforceable, and/or will not be infringed by Barr. Barr's notice also informed Ortho-McNeil that Barr seeks approval to market the ANDA products before the '560 patent expires. This action is being filed within 45 days after Ortho-McNeil received Barr's notice.

Patent Infringement Claim

16. Ortho-McNeil restates and incorporates by reference the allegations of the foregoing paragraphs 1-15 as though fully set forth herein.

17. Because Barr seeks approval of its ANDA before the '560 patent expires in order to engage in the commercial manufacture, use or sale of a drug, the use of which is claimed in the '560 patent, Barr has infringed the '560 patent pursuant to 35 U.S.C. § 271(e)(2)(A).

18. Ortho-McNeil is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Barr's ANDA be a date that is not earlier than the expiration date of the '560 patent.

19. Upon information and belief, Barr was aware of the existence of the '560 patent and was aware that the filing of its ANDA and certification with respect to the '560 patent constituted an act of infringement of that patent.

20. Upon information and belief, Barr's statement of the factual and legal bases for its opinion regarding the alleged non-infringement of the '560 patent is devoid of an objective good faith basis in either the facts or the law.

21. Ortho-McNeil will be irreparably harmed if Barr is not enjoined from infringing or actively inducing or contributing to infringement of the '560 patent.

22. Ortho-McNeil does not have an adequate remedy at law.

23. This case is an exceptional one, and Ortho-McNeil is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, plaintiff Ortho-McNeil respectfully requests that:

a. Judgment be entered that defendant Barr has infringed the '560 patent by submitting the aforesaid ANDA;

b. Judgment be entered that Ortho-McNeil is entitled to its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

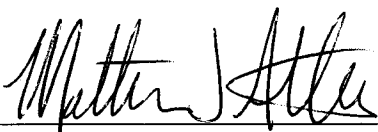
c. To the extent Barr has committed any acts with respect to the methods claimed in the '560 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), Ortho-McNeil be awarded damages for such acts, which this Court should treble pursuant to 35 U.S.C. § 284;

d. A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Barr, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any method of treatment as claimed in the '560 patent, or from actively inducing or contributing to infringement of the '560 patent;

e. An order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 76-448 be a date that is not earlier than the expiration date for the '560 patent; and

f. An order be issued for such other and further relief as the Court may deem just and proper under the circumstances.

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By:  _____

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Dated: December 15, 2006

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EXHIBIT A



US007125560B2

(12) **United States Patent**
Thakur et al.

(10) **Patent No.: US 7,125,560 B2**
(45) **Date of Patent: Oct. 24, 2006**

(54) **PHARMACEUTICAL COMPOSITION OF TOPIRAMATE**

(75) Inventors: **Madhav S. Thakur**, North Wales, PA (US); **Pramod M. Kotwal**, Blue Bell, PA (US); **Irwin S. Gibbs**, Huntington Valley, PA (US)

(73) Assignee: **Ortho-McNeil Pharmaceutical, Inc.**, Raritan, NJ (US)

(*) 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.: **10/748,764**

(22) Filed: **Dec. 30, 2003**

(65) **Prior Publication Data**

US 2004/0156901 A1 Aug. 12, 2004

Related U.S. Application Data

(62) Division of application No. 09/259,718, filed on Mar. 1, 1999, now Pat. No. 6,696,091.

(60) Provisional application No. 60/076,770, filed on Mar. 4, 1998.

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

(52) **U.S. Cl.** **424/441; 424/492**

(58) **Field of Classification Search** **424/493, 424/494, 497**

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,079,125 A	3/1978	Sipos
4,205,060 A	5/1980	Monsimer et al.
4,513,006 A	4/1985	Maryanoff et al.
4,568,559 A	2/1986	Nuwayser et al.
4,639,370 A	1/1987	Carli
4,800,087 A	1/1989	Mehta
4,851,226 A	7/1989	Julian et al.
4,882,169 A	11/1989	Ventouras
4,888,177 A	12/1989	Gergely et al.
4,892,740 A	1/1990	Takasima et al.
4,916,161 A	4/1990	Patell
4,985,252 A	1/1991	Jung et al.
4,994,260 A	2/1991	Kallstrand et al.
4,994,496 A	2/1991	Repasky et al.
5,008,117 A	4/1991	Calanchi et al.
5,013,716 A	5/1991	Cherukuri et al.
5,082,669 A	1/1992	Shirai et al.
5,084,278 A *	1/1992	Mehta 424/441
5,133,974 A	7/1992	Paradissis et al.
5,147,655 A	9/1992	Ibsen
5,206,030 A	4/1993	Wheatley et al.
5,215,755 A	6/1993	Roche et al.
5,260,072 A	11/1993	Roche et al.
5,275,823 A	1/1994	Frace et al.
5,286,489 A	2/1994	Tsau et al.
5,354,566 A	10/1994	Addesso et al.
5,393,333 A	2/1995	Trouve

5,401,502 A	3/1995	Wunderlich et al.
5,405,616 A	4/1995	Wunderlich et al.
5,409,711 A	4/1995	Mapelli et al.
5,417,985 A	5/1995	Coutel et al.
5,425,742 A	6/1995	Jay
5,460,825 A	10/1995	Roche et al.
5,489,436 A	2/1996	Hoy et al.
RE35,200 E	4/1996	Lehmann et al.
5,560,913 A	10/1996	Kupper et al.
5,578,316 A	11/1996	Bhardwaj et al.
5,607,697 A	3/1997	Alkire et al.
5,633,015 A	5/1997	Gilis et al.
5,641,513 A	6/1997	Lech et al.
5,648,096 A	7/1997	Gander et al.
5,705,183 A	1/1998	Phillips et al.
5,760,007 A	6/1998	Shant et al.
5,795,909 A	8/1998	Shashova et al.

FOREIGN PATENT DOCUMENTS

DE	3012136 C2	10/1981
DE	3943242 A1	6/1990
DE	4201179 A1	7/1993
EP	138441 B	4/1985
EP	0287 488 B1	10/1988
EP	0350701 A2	1/1990
EP	0446753 B1	9/1991
EP	0317274 B1	3/1993
EP	0459695 B1	3/1995
GB	2025227 B	1/1980
GB	2153676	8/1985
GB	2153677 B	8/1985
WO	88/03795 A1	6/1988
WO	WO 88/03795 A1	6/1999

OTHER PUBLICATIONS

D.R. Doose et al.—50th Annual meeting of the American Epilepsy society, san Francisco, 1996.
The Physician's desk Reference (52nd Ed., Medical Economics Company) p. 2058.
Taber's Cyclopedia Medical Dictionary (17th Ed., F.A Davis Co.) pp. 532-534.
Janssen_Cilag Farmaceutica, LDA, "Topamax (summary of Product Characteristics of Topiramate, approved by the Portuguese Health Authorities)", 20 ABR. 2004, Comunica No. 19, p. 11-12.

(Continued)

Primary Examiner—Jyothsna Venkat
(74) *Attorney, Agent, or Firm*—Mary Appollina

(57) **ABSTRACT**

The invention is directed to a pharmaceutical composition of topiramate, an anticonvulsant which is useful for treating epilepsy. More specifically, the present invention provides a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets. Processes for preparing the pharmaceutical composition are also described.

5 Claims, No Drawings

US 7,125,560 B2

Page 2

OTHER PUBLICATIONS

European Commission, Directorate General III—Industry Pharmaceuticals and Cosmetics, “Guidelines—Medicinal Products for Human Use, Quality and Biotechnology”, The Rules Governing Medicinal Product in European Union, vol. 3A, pp. 143-151, 1998.
European Commission, Directorate General III—Industry Pharmaceuticals and Cosmetics, “Guidelines—Medicinal Products for Human Use, Quality and Biotechnology”, The Rules Governing Medicinal Product in European Union, vol. 3A, pp. 127-141, 1998.
Simposium Terapeutico, Enciclopedia de Especialidades Farmaceuticas Portuguesas “Monography of TOPAMAX”, pp. 1015-1055, 2001.

Simposium Terapeutico, Enciclopedia de Especialidades Farmaceuticas Portuguesas, “Monography of TOPAMAX”, pp. 1015-1017, 2002.

Simposium Terapeutico, Enciclopedia de Especialidades Farmaceuticas Portuguesas, “Monography of TOPAMAX”, pp. 974-977, 2003.

Simposium Terapeutico, Enciclopedia de Especialidades Farmaceuticas Portuguesas, “Monography of TOPAMAX”, pp. 986-989, 2004.

* cited by examiner

US 7,125,560 B2

1

PHARMACEUTICAL COMPOSITION OF TOPIRAMATE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a divisional of U.S. application Ser. No. 09/259,718, filed Mar. 1, 1999, now U.S. Pat. No. 6,696,091 which claims priority from U.S. provisional application Ser. No. 60/076,770, filed Mar. 4, 1998, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides a solid dosage formulation of topiramate and process for producing the solid dosage formulation. More particularly, the solid dosage formulation comprises core particles which are coated with a taste mask coating to provide coated particles which can be sprinkled onto food to ease administration to patients who have difficulty swallowing tablets or capsules, e.g., pediatric patients.

BACKGROUND OF THE INVENTION

The pharmaceutical industry employs a variety of dosage formulations for orally administering medicinal agents to patients. Typical formulations for oral administration include liquid solutions, emulsions, or suspensions, as well as solid forms such as capsules or tablets (as used herein, the term "tablet" means any shaped and compressed solid dosage form, including caplets). Since these conventional solid dosage formulations are usually intended for adults who can easily swallow large tablets whole, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except for the provision of means to prevent the taste from being apparent during the short time that the medicine is in the mouth. Such means may include the provision of an appropriate coating on the tablet, the use of a capsule form (the gelatin outer shell of the capsule keeps the active ingredient inside until the capsule has been swallowed), or simply firmly compressing a tablet so that it will not begin to disintegrate during the short time that it is intended to be in the mouth.

Children, older persons, and many other persons have difficulty swallowing whole tablets and even capsules. Therefore, it is often desirable to provide the medicine either in liquid form or in a chewable solid form or an alternative solid form, e.g., small particles which can be sprinkled onto soft food and swallowed intact with the food, in addition to the tablet or capsule intended to be swallowed whole. Even where the medicine can be formulated as a liquid, it is desirable to provide a chewable solid form or an alternative solid form such as microspheres which can be sprinkled onto soft food (e.g., baby food) because it is often more convenient and easier to administer.

A major requirement of any such solid form is that it must be palatable, since an unpalatable formulation greatly increases the risk of a patient neglecting to take a medication. A further requirement of any solid dosage form is that it must be bioavailable; that is, once the formulation reaches the stomach, the individual particles should release the active ingredient rapidly and completely to ensure that substantially all of the active ingredient is absorbed. In cases where the active ingredient is particularly unpalatable and somewhat unstable, it may be difficult, if not impossible, to

2

identify a solid form that fulfills both of these requirements (i.e., palatable and bioavailable).

A number of references are known which describe pharmaceutical compositions of unpalatable medicinal agents which are coated with a taste masking coating in order to hide the unpleasant taste. Julian et al., in U.S. Pat. No. 4,851,266, describe chewable medicament tablets made by coating granules of a medicament (especially, acetyl p-aminophenol) with a blend of cellulose acetate or cellulose acetate butyrate and polyvinyl pyrrolidone (also known as "PVP" and referred to hereinafter by its United States Pharmacopeia (USP) name as "povidone"). Mehta, in U.S. Pat. No. 5,084,278, discloses a pharmaceutical composition comprised of a pharmaceutical core of an active dose of a compound and a microencapsulating polymer which coats the pharmaceutical core and is capable of taste-masking the active compound. Bhardway, et al., in U.S. Pat. No. 5,578,316, describe medicament cores coated with methacrylate ester copolymers which mask the bitter and unpleasant taste of the medicament.

A variety of chlorosulfate and sulfamate esters of 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose, and their anticonvulsant activity in mammals, and thus their utility in treating diseases such as epilepsy and glaucoma, are described in U.S. Pat. No. 4,513,006. More specifically, the compound 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate, hereinafter referred to as "topiramate", is presently available for marketing as a tablet product in strengths of 25, 50, 100, 200, 300 and 400 mg as adjunctive therapy for the treatment of adults with partial onset seizures (TOPAMAX® (topiramate) tablets). Topiramate can be prepared following the processes disclosed in U.S. Pat. Nos. 4,513,006 and 5,387,700, and preferably, by the process described in Examples 1 to 3 of U.S. Pat. No. 5,387,700. Difficulty in identifying a chewable solid form of topiramate has ensued due to the extremely bitter taste of topiramate and problems associated with stability of the active agent, especially upon exposure to moisture and heat which are known to cause degradation of topiramate. Degradation of topiramate is readily detected by changes in physical appearance, i.e., discoloration to brown or black, and by the formation of sulfate ions which can be readily detected by standard techniques known to those of ordinary skill in the art (e.g., HPLC).

Accordingly, it is an object of the invention to provide a stable solid formulation of topiramate for use in children and other patients who have difficulty swallowing conventional solid forms (e.g., tablets, capsules) which is both palatable and bioavailable. It is a further object of the invention to provide a palatable solid formulation of topiramate that can be sprinkled onto soft food prior to consumption (i.e., a "sprinkle formulation") and which provides immediate release of the active ingredient in the stomach.

SUMMARY OF THE INVENTION

The present invention is directed to a process for forming a pharmaceutical composition comprising:

- (a) preparing core particles comprising an active agent of topiramate;
- (b) drying the core particles from step (a) to form dried core particles;
- (c) coating the dried core particles from step (b) with a taste masking mixture to form coated particles; and
- (d) drying the coated particles from step (c) to form the pharmaceutical composition wherein the amount of taste masking mixture ranges from about 7% by weight to about

US 7,125,560 B2

3

15% by weight of the pharmaceutical composition, preferably, about 9 to about 13%, and most preferably, about 11% by weight of the pharmaceutical composition.

In another aspect of the invention is a pharmaceutical composition comprising:

(a) core particles containing an active agent of topiramate, wherein the core particles have an initial particle size between about 0.100 mm and 2.5 mm; and

(b) a taste mask coating, wherein the taste mask coating comprises between about 7% by weight and about 15% by weight of the pharmaceutical composition, preferably, about 9 to about 13%, and most preferably, about 11% by weight of the pharmaceutical composition and wherein the coated particles of the pharmaceutical composition have a final particle size of about 0.100 mm to about 2.5 mm.

In one embodiment of the invention, the core particles comprise the active agent of topiramate and at least one excipient; preferably, the core particles comprise the active agent of topiramate, a binder and a diluent; more preferably, the core particles comprise the active agent of topiramate, a binder and sugar spheres.

In a class of the invention is a pharmaceutical composition comprising about 85 to about 93% by weight core beads, and about 7 to about 15% by weight of a coating; wherein the core beads comprise about 18 to about 21% by weight of topiramate, about 8 to about 11% by weight of povidone, and about 58 to about 61% by weight of sugar spheres; and the coating comprises about 6 to about 9% by weight of cellulose acetate, and about 2 to about 5% by weight of povidone.

In a subclass of the invention is the pharmaceutical composition comprising about 89% by weight of core beads and about 11% by weight coating, wherein the core beads comprise about 19.8% by weight topiramate, about 9.9% by weight povidone, and about 59.3% by weight sugar spheres; and the coating comprises about 7.2% by weight cellulose acetate and about 3.8% by weight povidone.

Illustrative of the invention are methods of treating convulsions and/or epilepsy in a mammal in need thereof which comprises administering to the mammal a therapeutically effective amount of any of the pharmaceutical compositions of the present invention.

Also included in the invention are methods of treating a condition selected from neuropathic pain, amyotrophic lateral sclerosis, acute ischemia, obesity, diabetes, psoriasis or bipolar disorder (including manic depression) in a mammal in need thereof which comprises administering to the mammal a therapeutically effective amount of any of the pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a solid dosage formulation of topiramate intended primarily for pediatric use, or for patients who cannot swallow tablets. More particularly, the solid dosage formulation is a sprinkle formulation comprising core particles of the active agent which is taste-masked with a second layer to obscure the extremely bitter taste of topiramate. The core particles can comprise topiramate alone, e.g., in granular or crystalline form, or topiramate and one or more excipients which are then formed into granules or beads by techniques known to one of ordinary skill in the art, e.g., roller compaction and comminution, extrusion-spheronization or other methods of forming granules or beads. The preferred solid dosage formulation of the present invention is in the form of microspheres which may be

4

sprinkled onto soft food (e.g., baby food) and swallowed by the patient along with the food.

In a preferred embodiment, three strengths, 15, 25, and 50 mg, are obtained from a single sprinkle formulation of topiramate coated onto sugar spheres using povidone as a binder, and taste-masked with a coating of cellulose acetate and povidone to form coated beads. The strengths are differentiated by means of differing fill weights and of proportional capsule sizes. That is, to aid in delivery of the appropriate dosage to the patient, an amount of coated beads sufficient to deliver the desired dose may be encapsulated into a capsule, for example, a size 0, size 1, or size 2 gelatin capsule consisting of a white body with a natural cap. Black pharmaceutical ink can be utilized to provide product identification information on the capsules. For pediatric patients, the capsules can be opened and the contents of the capsules sprinkled onto food and ingested; however, mature patients may swallow drug product in intact capsules, if desired.

In general, the process for the preparation of the sprinkle formulation includes a step in which core particles comprising granules, beads or crystals of topiramate, alone or in combination with one or more excipients, are coated with a taste masking mixture and then dried. The term "particles" as used herein refers to free flowing substances of any shape which are larger than a powder including crystals, beads (smooth, round or spherical particles) and granules. A variety of methods known to those of ordinary skill in the art of pharmaceutical sciences may be employed to prepare the core particles comprising the active agent of topiramate. In one method, granules or large single crystals of topiramate can be utilized as the core particles and coated with the taste masking mixture. The coated material formed from the granules or crystals of topiramate may then be compressed into chewable tablets, if desired, or sprinkled onto soft food and swallowed.

In a second approach, the active agent of topiramate (in powder form) is first placed in a fluidized bed equipment and thereafter, a spray binder solution or suspension comprised of, for example, povidone, starch, sugar, syrup, HPMC among other excipients known to those of ordinary skill in the art in a pharmaceutically acceptable solvent (e.g., water, ethanol, acetone, among others) is sprayed onto the powder, formed into granules and then dried until the solvent is evaporated to provide the core particles. The drying temperature may vary over a broad range, but should not be so high as to render the active agent inactive. As a slight modification of this second approach, a suspension of topiramate and a binder in a pharmaceutically acceptable solvent is sprayed onto sugar spheres in a fluidized bed equipment and dried to provide core beads.

In a third method for forming the core particles, powdered or granular active agent, and diluent or bulking agent are mixed with water or a pharmaceutically acceptable solvent (e.g., water, ethanol) to form a wet mass. The mixture is mixed, e.g., in a Hobart mixer or other suitable mixer, until a wet mass or dough is formed. The wet mass is then placed in an extruder and extruded as a long thin strand. The mixture may then be dried and suitably comminuted or may be placed in a suitable spheronizer to make a pharmaceutical core that is round followed by drying. The drying temperature may vary over a broad range, but should not be so high as to render the active agent inactive.

Still another approach for forming the core particles is by roller compaction of topiramate, either alone or in combination with one or more excipients. For example, topiramate in powdered or granular form can be mixed with excipient to provide suitable binding and lubricity, for example micro-

US 7,125,560 B2

5

crystalline cellulose, magnesium stearate or talc among others, and then passed through a compactor to compact the mixture into a mass. The mass is then passed through a size reduction machine and reduced to a suitable particle size to provide the core particles.

As used herein, the term "topiramate" and "active agent of topiramate" are synonymous and are used interchangeably throughout the specification to refer to the compound 2,3:4,5-bis-O-(1-methylethylidene)- β -fructopyranose sulfamate which forms the active agent of the pharmaceutical compositions of the present invention. Topiramate and its use for treating epilepsy and glaucoma are described in U.S. Pat. No. 4,513,006. Topiramate can be synthesized according to the processes disclosed in U.S. Pat. Nos. 4,513,006 and 5,387,700, and preferably, according to the process of Examples 1-3 of U.S. Pat. No. 5,387,700.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

The term "excipient," as used herein, refers to any inert substance which may be combined with an active agent for preparing convenient dosage forms, including, for example, diluents, binders, lubricants, disintegrants, colors, flavors and sweeteners.

Suitable diluents for use in the formulation and processes of the present invention include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, microcrystalline cellulose, kaolin, mannitol, sodium chloride, dry starch, powdered sugar and sugar spheres. In a preferred embodiment of the invention, sugar spheres (20-60 mesh, preferably, 20-40 mesh, most preferably, 20-24 mesh) are utilized as a diluent in the core beads. In a particularly preferred embodiment, sugar spheres NF (20/25 mesh) available from Crompton & Knowles Corporation as NU-PAREIL PG[®] are used.

Suitable binders for use in the instant formulation and processes include, but are not limited to synthetic gums such as hydroxypropyl methylcellulose ("HPMC"), povidone, carboxymethylcellulose, ethylcellulose and methylcellulose, starch, pregelatinized starch, gelatin, sugars (e.g., molasses) and natural gums (e.g., acacia gum, sodium alginate, panwar gum). Preferably, povidone (especially, Povidone USP) is used as the binder. In a particularly preferred embodiment, the povidone is PLASDONE[®] (K29/32) supplied by ISP Technologies, Inc. as a manufacturer of GAF products.

Disintegrants which can be utilized in the formulation and processes of the present invention include, but are not limited to, methylcellulose, cellulose, carboxymethylcellulose, croscarmellose sodium, magnesium aluminum silicate, povidone, starch, sodium starch glycolate, pregelatinized starch, alginic acid and guar gum. Preferably, the disintegrant is povidone. In a particularly preferred embodiment, the povidone is PLASDONE[®] (K29/32) supplied by ISP Technologies, Inc. as a manufacturer of GAF products.

Suitable taste masking agents which can be used in the formulation and processes include, but are not limited to, cellulose acetate, cellulose acetate butyrate, ethylcellulose, methylcellulose (including ethylcellulose and methylcellulose combinations), and a wide range of copolymers available under the tradename of Eudragits (Röhm Pharma of Darmstadt, Germany). In a preferred embodiment, the taste masking agent is cellulose acetate (Cellulose Acetate, NF).

6

A variety of solvents may be used as the first and second solvent in the processes for preparing the pharmaceutical composition. Suitable solvents include, but are not limited to, water, acetone, alcohols (e.g., methanol, ethanol, isopropanol), methylene chloride, ethyl acetate, methyl ethyl ketone, and mixtures thereof. In a preferred embodiment, the first solvent used for forming the core beads is water, and the second solvent used for coating the core beads with the taste masking mixture is an acetone-alcohol mixture, preferably, an acetone-ethanol mixture, more preferably, an acetone-dehydrated alcohol mixture.

In a preferred embodiment, a suspension of topiramate and a binder in a first solvent is sprayed onto sugar spheres (20-25 mesh) and dried to provide core beads. The core beads are then screened to remove fines and agglomerates. The core beads are coated again with a taste masking mixture and then dried. The taste masking mixture, which is sprayed onto the core beads, comprises a taste masking agent and a disintegrant dissolved or suspended in a second solvent, which may be the same or different from the first solvent. Coated beads are sifted to remove fines and agglomerates, prior to encapsulation.

In a particularly preferred embodiment of the process for preparing the sprinkle formulation, a suspension of topiramate in a solution of povidone in purified water is sprayed onto sugar spheres (20-25 mesh) and dried in a fluid bed processor equipped with a Wurster column. The ratio of topiramate:povidone utilized in the suspension can be 50:25, 50:30 or 50:35. Preferably, a 50:25 ratio of topiramate:povidone is used. The core beads then are screened to remove fines and agglomerates such that the core beads have a particle size between about 0.100 mm and about 2.5 mm, preferably, between about 0.5 mm and about 1.5 mm, most preferably, between about 0.710 mm and about 1.18 mm. The core beads are coated again with a taste masking mixture of cellulose acetate and povidone suspended in an acetone/alcohol mixture in a fluid bed unit equipped with a Wurster column, and dried. The ratio of cellulose acetate/povidone in the taste masking mixture can be 60/40, 50/50, 65/35 or 55/45; preferably, a 65/35 ratio of cellulose acetate/povidone is utilized. Coated beads are sifted to remove fines and agglomerates to provide a final particle size between about 0.100 mm and about 2.5 mm, preferably, between about 0.5 mm and about 1.5 mm, most preferably, between about 0.850 mm and about 1.18 mm. The coated beads are packaged (e.g., in capsules, sachets or other methods known to those of ordinary skill in the art) to deliver the desired amount of active ingredient to the patient.

When a particle size range is specified for the core and/or coated particles (e.g., between about 0.100 mm and about 2.5 mm), it is intended that at least 75%, preferably, 85%, and most preferably, 95% of the particles have a particle size falling within the specified range (e.g., about 0.100 mm and about 2.5 mm).

The invention will be described more specifically in terms of its preferred embodiment which is the preparation of a sprinkle formulation of topiramate. In the first step of the process, core beads are prepared by coating sugar spheres (20-25 mesh) with a suspension of topiramate and povidone in water. More particularly, the sugar spheres are placed in a fluidized bed coater and fluidized by a flow of warm air. The temperature of the air has not been found to be narrowly critical, and can vary over a wide range, however, the temperature should not be high enough to cause decomposition, sintering, or melting of the sugar spheres. When coating the sugar spheres with the topiramate/povidone suspension (preferably, a 50:25 ratio), a temperature from

US 7,125,560 B2

7

about 500 to 75° C. has been found to be suitable. The rate of air flow is adjusted so as to fluidize the sugar spheres. Such flow will vary depending on factors such as the specific equipment used, the size of the individual sugar spheres, the size of the charge of sugar spheres, the apparent specific gravity of the spheres, and other factors known to the worker in the arts relating to fluidized bed coating. After the sugar spheres have been fluidized, a previously prepared suspension of topiramate in a solution of povidone in water is sprayed onto the fluidized bed to provide the core beads. The air flow through the bed is continued until the amount of water remaining in the topiramate core beads has been substantially reduced. The core beads are actually dry to the touch within a very short time after the topiramate suspension has been sprayed onto the sugar spheres. However, the total drying time required to ensure that the water content has been reduced to the desired level may take much longer, depending on the temperature of the air, the size of the batch, and the like. Routine experimentation will suffice to determine the appropriate air temperatures and total times required in the fluidized bed coaters in individual cases. The core beads are sized through a sifter using 16 mesh and 25 mesh screens.

In the second step of the process, the core beads are coated with a taste masking mixture to provide the coated beads of the sprinkle formulation. More specifically, the core beads are placed in a fluidized bed coater and fluidized by a flow of warm air. The temperature of the air has not been found to be narrowly critical, and can vary over a wide range, keeping in mind the fact that the temperature should not be so high as to cause decomposition, sintering, or melting, of the topiramate core beads. When coating the topiramate core beads, a temperature of from 300 to 75° C. has been found to be suitable. The rate of air flow is adjusted so as to fluidize the core beads. Such flow will vary depending on factors such as the specific equipment used, the size of the charge of core beads, the size of the individual core beads, the apparent specific gravity of the core beads, and other factors known to the worker skilled in the arts of fluidized bed coating. After the core beads have been fluidized, a taste mask coating mixture is sprayed onto the fluidized bed. The taste mask coating mixture comprises a solution of cellulose acetate/povidone (preferably, in a 65:35 ratio) in an acetone-alcohol (preferably, acetone-dehydrated alcohol) solvent mixture. The air flow through the bed is continued until the amount of solvent remaining in the coating has been reduced to part per million levels. The coated beads are actually dried to the touch within a very short time after the coating solution has been sprayed onto the topiramate core beads. However, the total drying time required to ensure that the solvent content of the coating has been reduced to the level desired may take much longer, depending on the temperature of the air, the size of the batch and the like. Routine experimentation will suffice to determine the appropriate air temperature and total times required in the fluidized bed coaters in individual cases. The coated beads are then sized through a sifter using 16 mesh and 20 mesh screens.

A sprinkle formulation having satisfactory taste masking and bioavailability properties was obtained when the taste mask coating comprises about 7 to about 15% by weight of the final pharmaceutical composition. Preferably the taste mask coating comprises about 9% by weight to about 13% by weight, most preferably, about 11% by weight, of the pharmaceutical composition when dried.

8

Dissolution results in water indicative of bioavailability for the pharmaceutical composition having between 7 and 15% by weight taste mask coating are shown below in Table 1.

TABLE 1

DISSOLUTION RESULTS IN WATER					
Coating (%)	(% Dissolved)				
	10 min	20 min	30 min	45 min	60 min
7	35.0	72.9	91.2	98.4	99.2
9	26.8	58.1	84.3	97.7	100.8
11	21.7	52.3	79.1	97.3	99.7
13	15.5	40.9	66.3	91.4	98.8
15	12.5	35.3	59.7	85.6	96.6

To aid in delivery of the appropriate dosage to the patient, an encapsulation machine can be utilized to encapsulate an amount of coated beads to provide 15 mg, 25 mg and 50 mg strengths of topiramate into a size 2, 1 or 0 gelatin capsule, respectively.

While the use of fluidized bed coating has been described in some detail as one preferred method for making the core beads and the coated beads, other techniques for making the core and coated beads readily known to those of ordinary skill in the art may be used. Such other techniques include various microencapsulation techniques such as coacervation and solvent evaporation.

In a particularly preferred embodiment, the ingredients and amounts of each ingredient used to prepare the topiramate sprinkle bead formulation are provided in Table 2.

TABLE 2

TARGET COMPONENT/COMPOSITION					
INGREDIENT	REFERENCE	ROLE	Unit Dosage Strength (mg)		
			50 mg	25 mg	15 mg
Topiramate		Active	50.0	25.0	15.0
Povidone	USP	Binding Agent	25.0	12.5	7.5
Purified Water ¹	USP	Process Aide	—	—	—
Sugar Spheres, 20-25 mesh	NF	Core Bead	150.0	75.0	45.0
Cellulose Acetate	NF	Film Coat	18.076	9.038	5.423
Povidone	USP	Film Coat	9.733	4.8665	2.9199
Acetone ¹	NF	Process Aide	—	—	—
Dehydrated Alcohol ¹	USP	Process Aide	—	—	—
Gelatin Capsules	Type IV	Drug Product Holder	one unit (Size 0)	one unit (Size 1)	one unit (size 2)
Printing Ink		Identifier			

¹Essentially removed during drying.

The strengths of topiramate sprinkle capsules, 15, 25 and 50 mg are obtained from a single formulation of topiramate-coated beads by encapsulating the proportionate amounts of coated beads in appropriately sized and marked capsules. Table 3 provides a batch formula for a production batch of topiramate sprinkle bead formulation.

TABLE 3

INGREDIENT	BATCH FORMULATION TARGETED FORMULATION		
	TARGET (kg)	RANGE(kg)	RANGE (%)
<u>CORE BEADS</u>			
Topiramate	37.5	—	—
Povidone, USP	18.75	±0.09375	±0.5%
Purified Water, USP ¹	93.75	±0.9375	±1.0%
Sugar Sphere, NF 20–25 mesh	112.50	—	—
Core Bead Batch Size	168.75		
<u>COATED BEADS</u>			
Core Beads	150.00		
Cellulose Acetate, NF	12.051	±0.12051	±1.0%
Povidone, USP	6.489	±0.06489	±1.0%
Acetone, NF ¹	120.00	±1.2%	±1.0%
Dehydrated Alcohol, USP ¹	30.00	±0.3%	±1.0%
Coated Bead Batch Size	168.54		
<u>GELATIN CAPSULES</u>			
Gelatin			
Print Ink			

¹Essentially removed during drying.

A comparison of dissolution rates in water between TOPAMAX® 100 mg tablets and topiramate sprinkle capsule formulations, 25 and 50 mg dosages (according to the specifications of Table 2) are shown in Table 4.

TABLE 4

Product	DISSOLUTION COMPARISON			
	% Label Dissolved (mean)			
	10 min	20 min	30 min	45 min
100 mg Tablet	85.0 (79–89)	92.6 (89–96)	96.4 (93–99)	—
25 mg Sprinkle	19.7 (17–22)	51.4 (48–55)	75.0 (71–80)	94.7 (90–99)
50 mg Sprinkle	17.8 (17–19)	48.1 (45–50)	71.3 (69–73)	93.5 (91–96)

The stability of the sprinkle formulation of the present invention was compared to TOPAMAX® (topiramate) tablets by storing both formulations in controlled stability chambers for the purpose of determining the stability profile for the two products. Samples were stored at 30° C. The sprinkles were stored at 60% relative humidity (RH); relative humidity for the tablet batches was either controlled at 35% RH or was not controlled, but, in any event, was well below 60% RH. Data were collected for assay (amount of drug remaining), sulfate and sulfamate, physical appearance at selected time intervals, e.g., 18 months, 24 months. Physical appearance, i.e., discoloration to brown or black, and amount of sulfate detected are good indicators of degradation of the active agent (topiramate). For each mole of topiramate that degrades, a molar equivalent of inorganic impurity (sulfate/sulfamate) is formed. The presence of inorganic impurity is readily determined by one of ordinary skill in the art using standard techniques, e.g., HPLC.

At 18 months, some instability was detected by appearance data for the tablets, while the sprinkle formulation showed no signs of instability/degradation. Clear signs of

degradation were apparent by appearance and sulfate data for the tablets at 24 months. After 24 months of storage at 30 degrees 60% RH, the 25 and 50 mg strengths of sprinkle capsules remained stable while the 15 mg strength showed instability. At 25 degrees 60% RH storage for 24 months, all three strengths of the sprinkle formulation remained stable.

It is known that moisture accelerates the degradation of topiramate. It has now been unexpectedly found that the coating used to taste mask the topiramate core beads also provides a barrier to the absorption of moisture, and therefore, improves on the stability of the sprinkle formulation. For storage of the tablets, it was necessary to put a desiccant into the bottles to stabilize the tablet formulation. However, there is no need for a desiccant for the sprinkle formulation. In addition, the capsules which are used to ease delivery of the appropriate dosage of sprinkles contain more than 10% moisture by weight, and yet, this moisture does not accelerate the degradation of topiramate because of the taste mask coating for the sprinkles.

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples.

EXAMPLE 1

Preparation of Core Beads

Ingredient	Batch Amount (kg)
Topiramate	37.50
Povidone, USP	18.75
Sugar Spheres, NF (20–24 mesh)	112.50
Purified Water, USP	93.70

Batch amounts of each of the core bead ingredients were accurately weighed out. In a jacketed kettle (approximately 60 gallons) equipped with a sweeper, a homogenizer (Silverson or equivalent) and a mixer (LIGHTNIN® or equivalent) was placed the appropriate batch amount of purified water, USP. The batch amount of Povidone, USP was added and the resulting mixture mixed for a minimum of 15 minutes to disperse the povidone in the purified water. The topiramate (37.50 kg) was added and the mixture mixed for a minimum of 15 minutes to disperse. Water was passed through the jacket. Using the mixer and homogenizer, the topiramate suspension was homogenized for approximately 90 minutes (range: 80–100 minutes). Stirring was continued through the steps which follow for preparing the core beads.

A pump (Masterflex or equivalent) was prepared with three pump heads for spraying. The batch quantity of sugar spheres, NF was charged to a fluid bed (Glatt Fluid Bed equipped with a 32 inch Wurster column, 3 guns with 2.2 mm nozzles, or equivalent). The sugar spheres were fluidized and the topiramate suspension sprayed through the nozzles (approximate spray rate: 1 kg/min; approximate spray time: 2.25 hours) according to the parameters shown in Table 5.

TABLE 5

Operating Function	Operating Parameter
Air Flow	2400 CFM (range: 1900–2900 CFM)
Inlet Air Temperature	60° C. (range: 50° C.–70° C.)
Bed Temperature	40° C. (range: 38° C.–45° C.)
Atomization Air	3 bar (range: 2.7–3.5 bar)

11

The core beads were dried at 60° C. for at least 15 minutes (range: 15–18 minute) after the bed temperature had reached 60° C. (range: 55° C.–65° C.) according to the parameters provided in Table 6.

TABLE 6

Operating Function	Operating Parameter
Air Flow	2100 CFM (range: 1800–2200 CFM)
Inlet Air Temperature	60° C. (range: 50° C.–70° C.)
Atomization Air	1 bar (range: 1–2 bar)

The core beads were then sized through a 48" sifter (Sweco or equivalent), using 16 mesh and 25 mesh screens to remove fines and agglomerates.

EXAMPLE 2

Preparation of Coated Beads

Ingredient	Batch Amount (kg)
Topiramate —Core Beads	150.00
Cellulose Acetate, NF	12.051
Povidone, USP	6.489
Acetone, NF	120.00
Dehydrated Alcohol, USP	30.00

The batch quantities of Acetone, NF and Dehydrated Alcohol, USP were transferred to a suitable stainless steel tank and mixed. The batch quantity of Povidone, USP was added using a suitable mixer (LIGHTNIN® or equivalent). The batch quantity of Cellulose Acetate, NF was added at the vortex while mixing with a suitable mixer and the coating solution was checked visually for clarity.

The 16/25 mesh topiramate core beads (150 kg) from Example 1 were fluidized in a Glatt Fluid Bed processor equipped with a Wurster column (or equivalent). The core beads were sprayed with the coating solution until the entire quantity of coating solution was exhausted. The coated beads were dried at approximately 60° C. for a minimum of 30 minutes (range: 28–32 minutes). Operating parameters are shown in Table 7.

TABLE 7

Operating Ranges for Spraying/Drying	
Parameter	Operating Range
Inlet Air Flow	1500–3000 CFM
Inlet Air Temperature	30° C.–70° C.
Atomization Air	1–4 bars
Bed Temperature	30° C.–70° C.

A Sweco Sifter (or equivalent equipment) was fitted at the top with a 16 mesh screen and at the bottom with a 20 mesh screen. The entire batch of coated beads was sieved and coated beads outside the 16–20 mesh range discarded.

12

EXAMPLE 3

Encapsulation of Coated Beads

5 An encapsulation machine (H&K Encapsulator or equivalent) was prepared with a bead filler attachment and the coated beads from Example 2 encapsulated.

Target fill weights were determined by assay of the coated beads prior to encapsulation. Variability of the fill weight was controlled by weight sorting, which is required for the 15 mg strength, but optional and employed as necessary for the 25 and 50 mg strengths. A KKE sorting machine (or equivalent) was used to weigh the filled capsules when weight sorting was employed. Filled capsules not meeting the acceptable weight range were discarded by the sorter.

15 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

1. A method of treating convulsions in a mammal in need thereof which comprises administering to the mammal a therapeutically effective amount of a pharmaceutical composition comprising

(a) core particles containing an active agent of topiramate, a binder and a diluent wherein the diluent is sugar spheres and wherein the core particles have an initial particle size between about 0.710 mm and 1.18 mm; and

(b) a taste mask coating, wherein the taste mask coating comprises between about 9% by weight and about 13% by weight of the pharmaceutical composition and wherein the coated particles of the pharmaceutical composition have a final particle size between about 0.850 mm and 1.18 mm; and wherein the coated particles are sprinkled onto soft food and swallowed.

2. The method of claim 1, wherein the taste mask coating comprises about 11% by weight of the pharmaceutical composition.

3. The method of claim 1, wherein the binder is selected from povidone, HPMC, sodium alginate, panwar gum, acacia gum, gelatin, sugar, molasses, starch, pregelatinized starch, methylcellulose, ethylcellulose or carboxymethylcellulose; and the taste mask coating comprises a taste masking agent and a disintegrant, wherein the taste masking agent is selected from cellulose acetate, methylcellulose, ethylcellulose, a Eudragit or cellulose acetate butyrate; and the disintegrant is selected from povidone, cellulose, carboxymethylcellulose, croscarmellose sodium, magnesium aluminat silicate, starch, sodium starch glycolate, pregelatinized starch, alginic acid or guar gum.

4. The method of claim 3, wherein the binder is povidone, the taste masking agent is cellulose acetate and the disintegrant is povidone.

5. The method of claim 4, wherein the coated particles of the pharmaceutical composition are encapsulated.

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