US006217904B1

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

(10) **Patent No.: US 6,217,904 B1**
(45) **Date of Patent: Apr. 17, 2001**

(54) **PHARMACEUTICAL DOSAGE FORM FOR PULSATILE DELIVERY OF D-THREO-METHYLPHENIDATE AND A SECOND CNS STIMULANT**

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( * ) 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.: **09/544,382**

(22) Filed: **Apr. 6, 2000**

**Related U.S. Application Data**

(60) Provisional application No. 60/127,984, filed on Apr. 6, 1999.

(51) **Int. Cl.**[7] ..... **A61K 9/22**

(52) **U.S. Cl.** ..... **424/468**; 424/451; 424/452; 424/458; 424/464; 424/489; 424/490; 424/497

(58) **Field of Search** ..... 424/451, 452, 424/458, 464, 468, 489, 490, 497

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 4,627,850 | 12/1986 | Deters et al. | 604/892 |
| 4,713,247 | 12/1987 | Sakamoto et al. | 424/461 |
| 4,728,512 | 3/1988 | Mehta et al. | 424/458 |
| 4,777,049 | 10/1988 | Magruder et al. | 424/457 |
| 4,874,388 | 10/1989 | Wong et al. | 604/891.1 |
| 4,957,494 | 9/1990 | Wong et al. | 604/892.1 |
| 4,971,805 | 11/1990 | Kitanishi et al. | 424/494 |
| 5,023,088 | 6/1991 | Wong et al. | 428/473 |
| 5,110,597 | 5/1992 | Wong et al. | 424/438 |
| 5,204,116 | 4/1993 | Edgren et al. | 428/473 |
| 5,209,746 | 5/1993 | Balaban et al. | 604/892.1 |
| 5,221,278 | 6/1993 | Linkwitz et al. | 604/890.1 |
| 5,236,689 | 8/1993 | Wong et al. | 424/473 |
| 5,260,068 | 11/1993 | Chen | 424/451 |
| 5,260,069 | 11/1993 | Chen | 424/451 |
| 5,300,304 | 4/1994 | Sheth et al. | 424/490 |
| 5,308,348 | 5/1994 | Balaban et al. | 604/892.1 |
| 5,312,390 | 5/1994 | Wong | 604/892.1 |
| 5,340,590 | 8/1994 | Wong et al. | 424/473 |
| 5,348,748 | 9/1994 | Sheth et al. | 424/494 |
| 5,391,381 | 2/1995 | Wong et al. | 424/473 |
| 5,407,686 | 4/1995 | Patel et al. | 424/468 |
| 5,445,828 | 8/1995 | Pozzi et al. | 424/476 |
| 5,456,679 | 10/1995 | Balaban et al. | 604/892.1 |
| 5,472,708 * | 12/1995 | Chen | 424/451 |
| 5,498,255 | 3/1996 | Wong | 604/892.1 |
| 5,499,979 | 3/1996 | Wong et al. | 604/892.1 |
| 5,508,040 | 4/1996 | Chen | 424/451 |
| 5,531,736 | 7/1996 | Wong et al. | 604/892.1 |
| 5,773,478 | 6/1998 | Richards et al | 515/649 |
| 5,801,271 | 9/1998 | Seido et al. | 560/29 |
| 5,837,284 | 11/1998 | Mehta et al. | 424/459 |
| 5,859,249 | 1/1999 | Seido et al. | 546/235 |
| 5,874,090 | 2/1999 | Baker et al. | 424/400 |

FOREIGN PATENT DOCUMENTS

WO 98/06380 2/1998 (WO) .

OTHER PUBLICATIONS

Aoyama et al. (1990), Kinetic Analysis of Enantiomers of *threo* —Methylphenidate and Its Metabolite in Two Healthy Subjects After Oral Administration as Determined by a Gas Chromatographic—Mass Spectrometric Method, Journal of Pharmaceutical Sciences 79(6):465–469.

Aoyama et al. (1993), "Nonlinear Kinetics of *threo*—Methylphenidate Enantiomers in a Patient with Narcolepsy and in Healthy Volunteers," *European Journal of Clinical Pharmacology 44*:79–84.

Aoyama et al. (1994), "Stereospecific Distribution of Methylphenidate Enantiomers in Rat Brain: Specific Binding to Dopamine Reuptake Sites," *Pharmaceutical Research* 11(3):407–411.

Aoyama et al. (1994), "Pharmacokinetics and Pharmacodynamics of (+)–*threo*–Methylphenidate Enantiomer in Patients with Hypersomnia," *Clinical Pharmacology & Therapeutics* 55(3):270–276

Conte et al. (2000), "A Flexible Technology for the Linear, Pulsatile and Delayed Release of Drugs, Allowing for Easy Accommodation of Difficult In Vitro Targets," *Journal of Controlled Release* 64:263–268.

Ding et al. (1994), "Pharmacokinetics and In Vivo Specificity of [$^{11}$C]*dl–threo*–Methylphenidate for the Presynaptic Dopaminergic Neuron," *Synapse* 18:152–160.

Ding et al. (1995), "Carbon–11–*d–threo*–Methylphenidate Binding to Dopamine Transporter in Baboon Brain," *The Journal of Nuclear Medicine* 36(12):2298–2305.

Ferris et al. (1978), "Comparison of the Effects of the Isomers of Amphetamine, Methylphenidate and Deoxypipradrol on the Uptake of l–[$^{3}$H] Norepinephrine and [$^{3}$H] Dopamine by Synaptic Vesicles from Rat Whole Brain, Striatum and Hypothalamus,"*The Journal of Pharmacology and Experimental Therapeutics*210(3):422–428.

(List continued on next page.)

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(57) **ABSTRACT**

Novel pharmaceutical dosage forms provide for pulsatile delivery of d-threo-methylphenidate and a second CNS stimulant, i.e., release encapsulated drug in spaced apart "pulses." The second CNS stimulant may be an analeptic agent or a psychostimulant, with analeptic agents preferred. The dosage forms may comprise capsules housing compressed tablets or drug-containing beads or particles, or may comprise a tablet with the first, second and optionally third dosage units each representing an integral and discrete segment thereof. Methods of treatment using the pharmaceutical dosage forms are provided as well.

**38 Claims, No Drawings**