US005837284A

United States Patent [19]

Mehta et al.

[11] **Patent Number: 5,837,284**

[45] **Date of Patent: Nov. 17, 1998**

[54] **DELIVERY OF MULTIPLE DOSES OF MEDICATIONS**

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[21] Appl. No.: **892,190**

[22] Filed: **Jul. 14, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 567,131, Dec. 4, 1995, abandoned, and a continuation-in-part of Ser. No. 583,317, Jan. 5, 1996, and a continuation-in-part of Ser. No. 647,642, May 15, 1996.

[51] **Int. Cl.**[6] **A61K 9/56**; A61K 9/54; A61K 9/58; A61K 9/22; A61K 31/21

[52] **U.S. Cl.** **424/459**; 424/458; 424/462; 424/468; 514/317

[58] **Field of Search** 424/458, 459, 424/462, 468; 514/317

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,794,001	12/1988	Mehta et al.	424/458
5,326,570	7/1994	Rudnic et al.	424/458
5,478,573	12/1995	Eichel et al.	424/480
5,500,227	3/1996	Oshlack et al.	424/476
5,639,476	6/1997	Oshlack et al.	424/658
5,672,360	9/1997	Sackler et al.	424/490

OTHER PUBLICATIONS

PDR, 46th ed. "Ritalin SR" pp. 880–881, 1992.

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[57] **ABSTRACT**

Dosage forms for oral administration of a methylphenidate drug are provided. The dosage forms provide a substantially immediate dose of methylphenidate upon ingestion, followed by one or more additional doses at predetermined times. By providing such a drug release profile, the dosage forms eliminate the need for a patient to carry an additional dose for ingestion during the day. The dosage forms and methods provided are useful in administering methylphenidate and pharmaceutically acceptable salts thereof, which generally require one or more doses throughout the day.

30 Claims, 2 Drawing Sheets

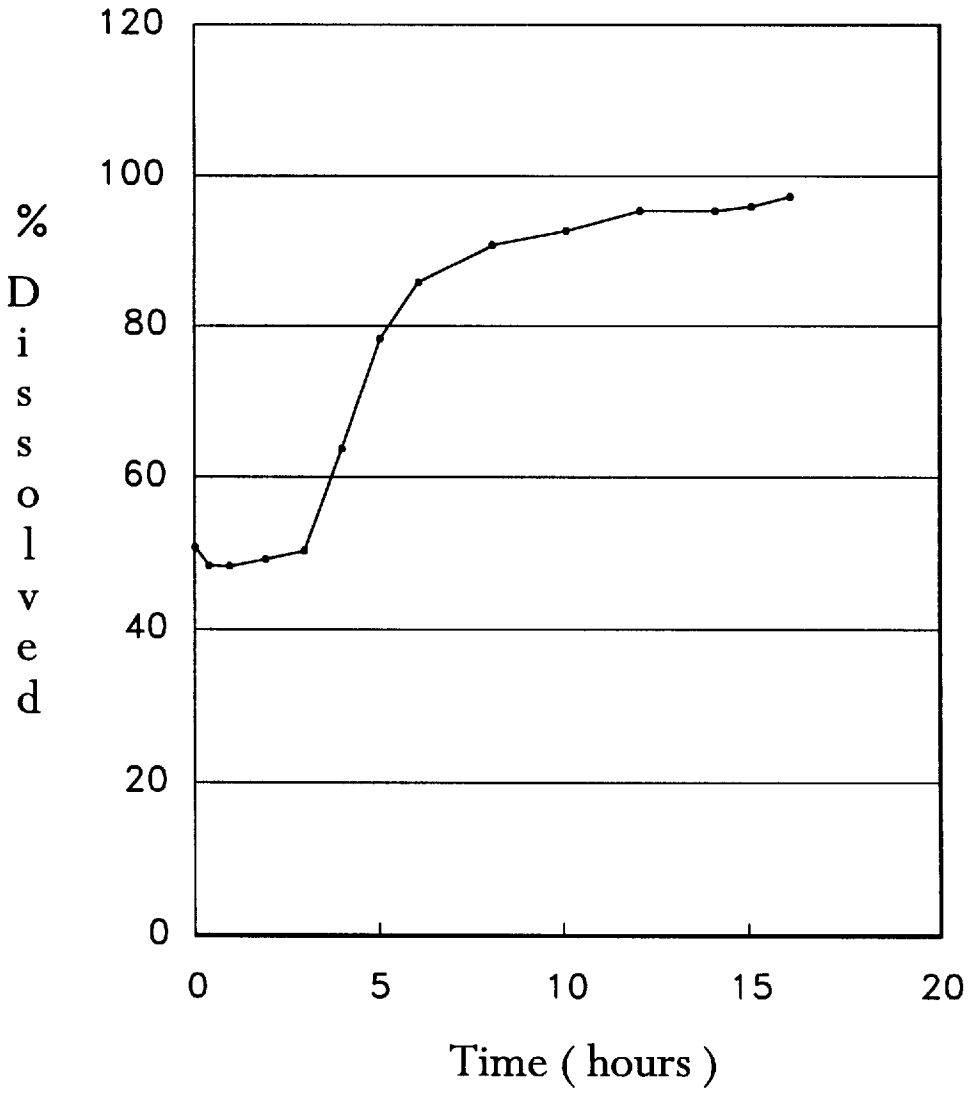


FIG. 1

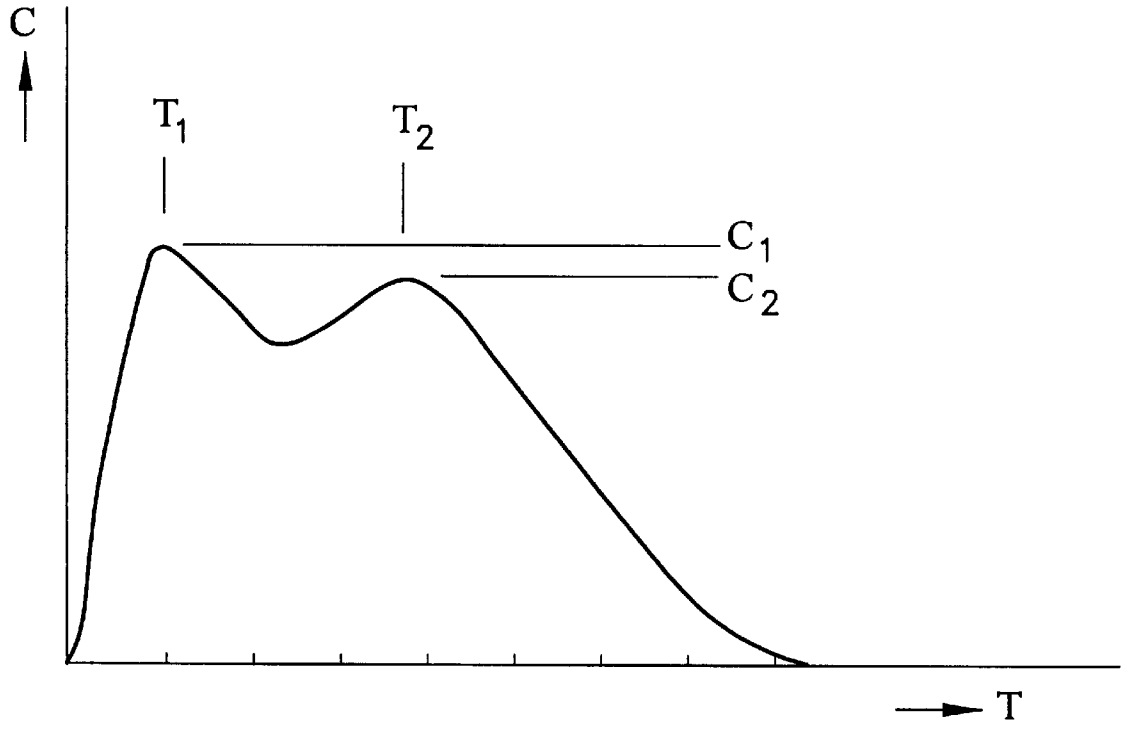


FIG. 2

DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of application Ser. No. 08/567,131, filed Dec. 4, 1995, now abandoned; application Ser. No. 08/583,317, filed Jan. 5, 1996; and application Ser. No. 08/647,642, filed May 15, 1996.

FIELD OF THE INVENTION

The present invention relates to improved dosing of medications. In particular, the present invention relates to improved dosing of a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit. The second, and any later, dose is time-delayed following administration. Based on predictable in vitro release times, the dosage forms can be formulated to deliver delayed doses in vivo at desired times.

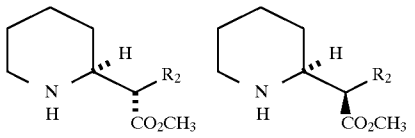
The dosage forms and methods of the present invention are particularly suitable for the administration of methylphenidate hydrochloride, and especially for the administration of a single isomer, d-threo-methylphenidate hydrochloride.

The administration of dosage forms which contain an immediate dosage and a delayed second dosage provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when methylphenidate is used to treat certain central nervous system disorders.

BACKGROUND OF THE INVENTION

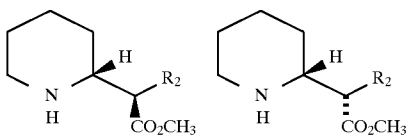
Attention Deficit Disorder (ADD), a commonly diagnosed nervous system illness in children, is generally treated with methylphenidate hydrochloride (available commercially as, e.g., Ritalin®). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by symptoms of hyperactivity, and is also treated with methylphenidate hydrochloride. Methylphenidate drugs have also been used to treat cognitive decline in patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS related conditions. See, e.g., Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995); Holmes et al., *J. Clin. Psychiatry* 50:5–8 (1989).

Methylphenidate exists as four separate optical isomers as follows:



l-threo

d-erythro



d-threo

l-erythro

wherein R_2 is phenyl. Pharmaceutically acceptable salts are generally administered clinically. Other phenidate drugs, which also can be administered according to the invention, include those in which the methyl group in the above structures is replaced by C_2–C_4 alkyl and R_2 is optionally substituted with C_1–C_4 alkyl.

Clinically, the threo pair of enantiomers of methylphenidate hydrochloride is generally administered for the treatment of ADD and ADHD. The hydrochloride salt is commonly referred to simply as "methylphenidate". Unless indicated otherwise, the term "methylphenidate" is used broadly herein to include methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride.

The threo racemate (pair of enantiomers) of methylphenidate is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines. Undesirable side effects associated with the use of the dl-threo racemate of methylphenidate include anorexia, weight loss, insomnia, dizziness and dysphoria. Furthermore, the racemate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation or ingestion, and thus carries a high potential for abuse.

Srinivas et al. studied the administration of dl-threo-, d-threo, and l-threo-methylphenidate to children suffering from ADHD, and reported that the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer (*Clin. Pharmacol. Ther.,* 52:561–568 (1992)). Therefore, while dl-threo-methylphenidate is generally used therapeutically, this racemate includes the l isomer which apparently makes no significant contribution to the pharmacological effectiveness of the drug, but likely contributes to the associated side effects. It is thus desirable to administer only the active d-threo form of the drug.

An additional problem is that children being treated with dl-threo methylphenidate must generally take one or more doses during the day. This creates a problem for school administrators who must store a controlled substance on school premises, with the associated risk that it may be stolen for illicit use. Furthermore, children may be traumatized by ridicule from peers when they must take medication at school.

Sustained release formulations of dl-threo methylphenidate have been developed, which provide for slow release of the drug over the course of the day. However, it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. In some studies, sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

There remains a need for methods for delivering methylphenidate with maximum effectiveness and minimal potential for abuse. Furthermore, it has been determined that there is a need for a dosage form which provides, in one administration, an initial release followed, at a predictable delay, by a second release, of maximally effective methylphenidate. This will eliminate the risk of theft or loss of the second dose, while minimizing undesirable side effects and maximizing ease of administration. The present invention is directed to these, as well as other, important ends.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts an in vitro time-concentration relationship (release profile) for certain preferred dosage forms in accordance with the invention.

FIG. **2** depicts a schematic representation of in vivo plasma concentration of a drug released according to the release profile shown in FIG. **1**.

SUMMARY OF THE INVENTION

The present invention provides, in one embodiment, a therapeutic composition for the oral administration of a methylphenidate drug comprising a dosage form containing two groups of particles, each containing the methylphenidate drug. The term "particles", as used herein, includes pellets, granules, and the like. The first group of particles provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles can also comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, of the methylphenidate drug, in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. If desired, one or more additional doses may be delivered by additional particles, coated in a similar manner, but with a sufficient amount of ammonio methacrylate copolymer coating to provide the dosage after an additional delay. Methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride, can be prepared into the dosage forms of the invention.

In one embodiment of the present invention, the first group of particles comprises a methylphenidate drug and provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles may comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the particles of the methylphenidate drug in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion.

For example, the first group of particles can comprise a pharmaceutically acceptable salt of methylphenidate, such as methylphenidate hydrochloride, in powder form, or coated or uncoated particles containing the methylphenidate salt. The amount of methylphenidate salt in each group of particles can vary, depending upon the dosage requirements of the patient to whom the drug is to be administered. Generally, the daily dosage requirement for methylphenidate drugs is from about 1 mg to about 50 mg per day, preferably from about 2 mg to about 20 mg, and more preferably from about 2.5 to about 12 mg per day. The actual dosage to be administered will be determined by the attending physician as a matter of routine. Thus, depending upon the amounts of coating and/or and optional excipients and other additives, the amount of methylphenidate drug can be, for example, from about 2% to about 99% by weight of the first group of particles. In addition to the methylphenidate drug, the second group of particles comprises a filler, such as a hydrophobic filler, one or more ammonio methacrylate copolymers, and optional excipients and other additives. The filler can be present in an amount of, for example, from about 35% to about 45%, by weight, based on the total weight of the second group of particles.

Another embodiment of the present invention provides a method for treating disease, such as, for example, ADD, ADHD, or AIDS-related dementia, in a patient in need of treatment. This treatment comprises administering to the patient a dosage form providing once-daily oral administration of a methylphenidate drug such as methylphenidate hydrochloride. The dosage form comprises at least two groups of particles, each containing the methylphenidate drug. The first group of particles comprises from about 2% to about 99% by weight of the methylphenidate drug, depending upon desired the daily dosage, and provides a substantially immediate dose of methylphenidate upon ingestion by a mammal. The first group may comprise a coating and/or sealant. The second group of particles comprises coated particles. The coated particles comprise the methylphenidate drug in admixture with one or more binders, wherein the amount of methylphenidate drug is from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, and a coating comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion. The components of the two groups of particles can vary as described hereinabove. The initial dose can be administered separately from the delayed dose, if desired.

A further embodiment of the present invention provides dosage forms for the oral administration, in a single dosage form, of two doses of a pharmaceutically acceptable salt of d-threo-methylphenidate. The dosage forms comprise particles containing within their interiors from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, of the d-threo-methylphenidate salt, in admixture with one or more binders. The particles have a coating exterior to the methylphenidate salt, which comprises an ammonio methacrylate copolymer in a quantity sufficient to delay release of the d-threo-methylphenidate salt contained within by from about 2 hours to about 7 hours following administration. The dosage forms also comprise, exterior to the coating, an outer layer comprising from about 2% to about 99% by weight of the d-threo-methylphenidate salt, based on the weight of all components in the outer layer, to provide a substantially immediate dose of the d-threo-methylphenidate salt upon administration. The layer comprising the immediate dose of the d-threo-methylphenidate salt can, if desired, further comprise an outer sealant layer. If desired, the two doses of the d-threo-methylphenidate salt can be approximately equal.

The present invention also provides dosage forms providing plasma concentration profiles for methylphenidate having two maxima, temporally separated from each other by from about 2 hours to about 7 hours. Preferably, the magnitude of said maxima differs by no more than about 30 percent, more preferably by no more than about 20 percent, and most preferably by no more than about 10 percent.

"Methylphenidate" as used herein, includes all four optical isomers of the compound and all pharmaceutically acceptable salts thereof. When one or more particular isomers is contemplated, the isomer is indicated, as in d-threo, l-threo, etc. The combined threo isomers may be indicated simply as "threo " and the erythro isomers as "erythro ". For therapeutic use in treating conditions treatable by methylphenidate drugs, dl-threo methylphenidate hydrochloride is generally used, while d-threo methylphenidate hydrochloride is preferred according to the present invention.

As discussed, the four isomers have exhibited varying levels of therapeutic activity, and have been shown to differ generally in producing unwanted side effects. The present invention provides dosage forms which maximize therapeu-

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