US 20040197405A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0197405 A1

Devane et al. (43) Pub. Date: Oct. 7, 2004

(54) MULTIPARTICULATE MODIFIED RELEASE COMPOSITION

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(21) Appl. No.: **10/827,689**

(22) Filed: **Apr. 19, 2004**

Related U.S. Application Data

(63) Continuation of application No. 10/354,483, filed on Jan. 30, 2003, which is a continuation of application No. 10/331,754, filed on Dec. 30, 2002, which is a continuation of application No. 09/850,425, filed on May 7, 2001, now Pat. No. 6,730,325, which is a continuation of application No. 09/566,636, filed on May 8, 2000, now Pat. No. 6,228,398, which is a continuation of application No. PCT/US99/25632, filed on Nov. 1, 1999.

(60) Provisional application No. 60/106,726, filed on Nov. 2, 1998.

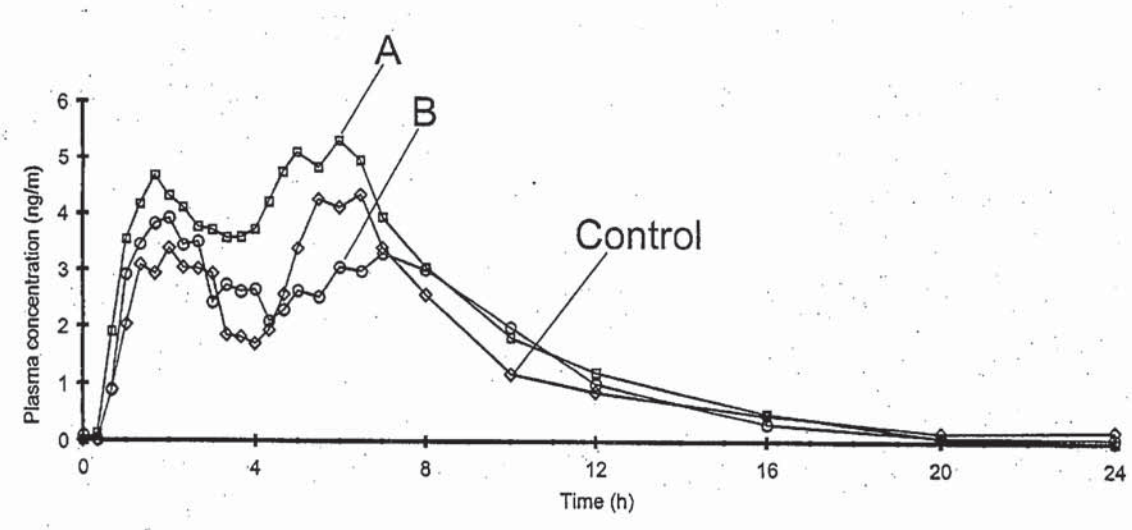
Publication Classification

(51) **Int. Cl.**[7] **A61K 9/26**; A61K 9/14

(52) **U.S. Cl.** **424/469**

(57) **ABSTRACT**

The invention relates to a multiparticulate modified release composition that in operation delivers an active ingredient in a pulsed or bimodal manner. The multiparticulate modified release composition comprises an immediate release component and a modified release component; the immediate release component comprising a first population of active ingredient containing particles and the modified release component comprising a second population of active ingredient containing particles coated with a controlled release coating; wherein the combination of the immediate release and modified release components in operation deliver the active ingredient in a pulsed or a bimodal manner. The invention also relates to a solid oral dosage form containing such a multiparticulate modified release composition. The plasma profile achieved by the multiparticulate modified release composition is advantageous in reducing patient tolerance to the active ingredient and in increasing patient compliance by reducing dosage frequency.



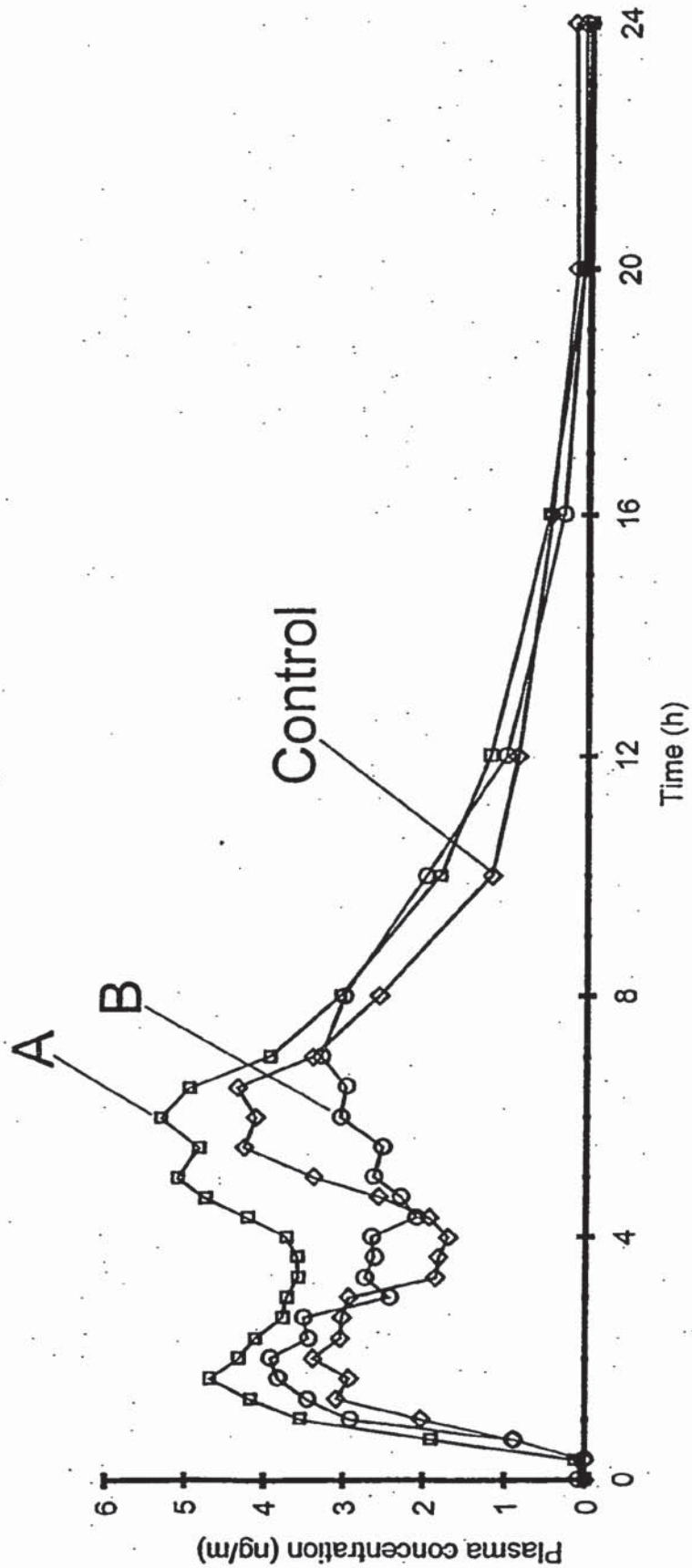


Figure 1

MULTIPARTICULATE MODIFIED RELEASE COMPOSITION

FIELD OF THE INVENTION

[0001] The present invention relates to a multiparticulate modified release composition. In particular the present invention relates to a multiparticulate modified release composition that in operation delivers an active ingredient in a pulsatile manner. The present invention further relates to solid oral dosage forms containing such a multiparticulate controlled release composition.

DESCRIPTION OF THE PRIOR ART

[0002] The plasma profile associated with the administration of a drug compound may be described as a "pulsatile profile" in which pulses of high active ingredient concentration, interspersed with low concentration troughs, are observed. A pulsatile profile containing two peaks may be described as "bimodal". Similarly, a composition or a dosage form which produces such a profile upon administration may be said to exhibit "pulsed release" of the active ingredient.

[0003] Conventional frequent dosage regimes in which an immediate release (IR) dosage form is administered at periodic intervals typically gives rise to a pulsatile plasma profile. In this case, a peak in the plasma drug concentration is observed after administration of each IR dose with troughs (regions of low drug concentration) developing between consecutive administration time points. Such dosage regimes (and their resultant pulsatile plasma profiles) have particular pharmacological and therapeutic effects associated with them. For example, the wash out period provided by the fall off of the plasma concentration of the active ingredient between peaks has been thought to be a contributing factor in reducing or preventing patient tolerance to various types of drugs.

[0004] Many controlled release drug formulations are aimed at producing a zero-order release of the drug compound. Indeed, it is often a specific object of these formulations to minimize the peak-to-trough variation in drug plasma levels associated with conventional frequent dosage regimes. However, some of the therapeutic and pharmacological effects intrinsic in a pulsatile system may be lost or diminished as a result of the constant or nearly constant plasma levels achieved by zero-order release drug delivery systems. Thus, a modified release composition or formulation which substantially mimics the release of frequent IR dosage regimes, while reducing the need for frequent dosing, is desirable.

[0005] A typical example of a drug which may produce tolerance in patients is methylphenidate. Methylphenidate, or .alpha.-phenyl-2-piperidine acetic acid methyl ester, is a stimulant affecting the central nervous and respiratory systems and is primarily used in the treatment of attention deficit disorder. After absorption from the gastrointestinal tract (GIT), drug effects persist for 3-6 hours after oral administration of conventional IR tablets or up to about 8 hours after oral administration of extended release formulations. The total dosage is typically in the range of 5-30 mg per day, in exceptional cases rising to 60 mg/day. Under conventional dosage regimes, methylphenidate is given and a second dose given before lunch. The last daily dose is preferably given several hours before retiring. Adverse effects associated with methylphenidate treatment include insomnia and the development of patient tolerance.

[0006] WO 98/14168 (Alza Corp.) teaches a dosage form and a method of administering methylphenidate in a sustained and constantly ascending rate. The dosage form disclosed comprises a plurality of beads comprising a hydrogel matrix with increasing amounts of the active ingredient therein, coated with varying amounts of a release rate controlling material. Appropriate-combinations of the active ingredient dose and the number and thickness coating layers can be selected to give an ascending release profile in which the plasma concentration of the active ingredient continually increases over a given period of time. In contrast to the present invention, an object of WO 98/14168 is to provide a dosage form to specifically avoid uneven blood levels (characterized by peaks and troughs) associated with conventional treatments using immediate release dosage formulations.

[0007] WO 97/03672 (Chiroscience Ltd.) discloses that methylphenidate exhibits a therapeutic effect when administered in the form of a racemic mixture or in the form of a single isomer (such as the RR d-threo enantiomer). Further, WO 97/03763 (Chiroscience Ltd.) discloses a sustained release formulation containing dtmp. This disclosure teaches the use of a composition comprising a coating through which the dtmp passes in order to attain sustained release and achieve serum levels (of the active ingredient) of at least 50% c.sub.max over a period of at least 8 hours. Thus, this formulation does not deliver the active ingredient in a pulsatile manner.

[0008] Shah et al., J Cont. Rel. (1989) 9:169-175 discloses that certain types of hydroxypropyl methylcellulose ethers compressed into a solid dosage form with a therapeutic agent may give a bimodal release profile. However, it was noted that while polymers from one supplier yielded a bimodal profile, the same polymers with almost identical product specifications obtained from a different source gave non-bimodal release profiles.

[0009] Giunchedi et al., Int. J. Pharm (1991) 77:177-181 discloses the use of a hydrophilic matrix multiple-unit formulation for the pulsed release of ketoprofen. Giunchedi et al. teach that ketoprofen is rapidly eliminated from the blood after dosing (plasma half-life 1-3 hours) and consecutive pulses of drug may be more beneficial than constant release for some treatments. The multiple-unit formulation disclosed comprises four identical hydrophilic matrix tablets placed in a gelatin capsule. Although the in vivo studies show two peaks in the plasma profile there is no well defined wash out period and the variation between the peak and trough plasma levels is small.

[0010] Conte et al., Drug Dev. Ind. Pharm, (1989) 15:2583-2596 and EP 0 274 734 (Pharmidea Srl) teach the use of a three layer tablet for delivery of ibuprofen in consecutive pulses. The three layer tablet is made up of a first layer containing the active ingredient, a barrier layer (the second layer) of semi-permeable material which is interposed between the first layer and a third layer containing an additional amount of active ingredient. The barrier layer and the third layer are housed in an impermeable

solving fluid while the third layer is only available after dissolution or rupture of the barrier layer. In such a tablet the first portion of active ingredient must be released instantly. This approach also requires the provision of a semi-permeable layer between the first and third layers in order to control the relative rates of delivery of the two portions of active ingredient. Additionally, rupture of the semi-permeable layer leads to uncontrolled dumping of the second portion of the active ingredient which may not be desirable.

[0011] U.S. Pat. No. 5,158,777 (E. R. Squibb & Sons Inc.) discloses a formulation comprising captopril within an enteric or delayed release coated pH stable core combined with additional captopril which is available for immediate release following administration. In order to form the pH stable core, chelating agents such as disodium edetate or surfactants such as polysorbate 80 are used either alone or in combination with a buffering agent. The compositions have an amount of captopril available for immediate release following oral administration and an additional amount of pH stabilized captopril available for release in the colon.

[0012] U.S. Pat. Nos. 4,728,512, 4,794,001 and 4,904,476 (American Home Products Corp.) relate to preparations providing three distinct releases. The preparation contains three groups of spheroids containing an active medicinal substance: the first group of spheroids is uncoated and rapidly disintegrates upon ingestion to release an initial dose of medicinal substance; the second group of spheroids is coated with a pH sensitive coat to provide a second dose; and the third group of spheroids is coated with a pH independent coat to provide to third dose. The preparation is designed to provide repeated release of medicinal substances which are extensively metabolized presystemically or have relatively short elimination half-lives.

[0013] U.S. Pat. No. 5,837,284 (Mehta et al) discloses a methylphenidate dosage form having immediate release and delayed release particles. The delayed release is provided by the use of ammonio methacrylate pH independent polymers combined with certain fillers.

[0014] Accordingly, it is an object of the present invention to provide a multiparticulate modified release composition containing an active ingredient which in operation produces a plasma profile substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially.

[0015] It is a further object of the invention to provide a multiparticulate modified release composition which in operation delivers an active ingredient in a pulsatile manner.

[0016] Another object of the invention is to provide a multiparticulate modified release composition which substantially mimics the pharmacological and therapeutic effects produced by the administration of two or more IR dosage forms given sequentially.

[0017] Another object of the present invention is to provide a multiparticulate modified release composition which substantially reduces or eliminates the development of patient tolerance to the active ingredient of the composition.

[0018] Another object of the invention is to provide a multiparticulate modified release composition in which a

upon administration and a second portion of the active ingredient is released rapidly after an initial delay period in a bimodal manner.

[0019] Another object of the invention is to provide a multiparticulate modified release composition capable of releasing the active ingredient in a bimodal or multi-modal manner in which a first portion of the active ingredient is released either immediately or after a delay time to provide a pulse of drug release and one or more additional portions of the active ingredient are released each after a respective lag time to provide additional pulses of drug release.

[0020] Another object of the invention is to provide solid oral dosage forms comprising a multiparticulate modified release composition of the present invention.

[0021] Other objects of the invention include provision of a once daily dosage form of methylphenidate which, in operation, produces a plasma profile substantially similar to the plasma profile produced by the administration of two immediate release dosage forms given sequentially and a method for treatment of attention deficit disorder based on administration of such a dosage form.

BRIEF DESCRIPTION OF THE INVENTION

[0022] The above objects are realized by a multiparticulate modified release composition having a first component comprising a first population of active ingredient-containing particles and a second component comprising a second population of active ingredient-containing particles. The active ingredient contained in the first and second components can be the same or different and active ingredient-containing particles of the second component are coated with a modified release coating. Alternatively or additionally, the second population of active ingredient containing particles further comprises a modified release matrix material. Following oral delivery, the composition in operation delivers the active ingredient or active ingredients in a pulsatile manner.

[0023] In a preferred embodiment of a multiparticulate modified release composition according to the invention the first component is an immediate release component.

[0024] The modified release coating applied to the second population of active ingredient containing particles causes a lag time between the release of active ingredient from the first population of active ingredient containing particles and the release of active ingredient from the second population of active ingredient containing particles. Similarly, the presence of a modified release matrix material in the second population of active ingredient containing particles causes a lag time between the release of active ingredient from the first population of active ingredient containing particles and the release of active ingredient from the second population of active ingredient containing particles. The duration of the lag time may be varied by altering the composition and/or the amount of the modified release coating and/or altering the composition and/or amount of modified release matrix material utilized. Thus, the duration of the lag time can be designed to mimic a desired plasma profile.

[0025] Because the plasma profile produced by the multiparticulate modified release composition upon administration is substantially similar to the plasma profile produced

sequentially, the multiparticulate controlled release composition of the present invention is particularly useful for administering active ingredients for which patient tolerance may be problematical. This multiparticulate modified release composition is therefore advantageous for reducing or minimizing the development of patient tolerance to the active ingredient in the composition.

[0026] In a preferred embodiment of the present invention, the active ingredient is methylphenidate and the composition in operation delivers the active ingredient in a bimodal or pulsed manner. Such a composition in operation produces a plasma profile which substantially mimics that obtained by the sequential administration of two IR doses as, for instance, in a typical methylphenidate treatment regime.

[0027] The present invention also provides solid oral dosage forms comprising a composition according to the invention.

[0028] The present invention further provides a method of treating an animal, particularly a human in need of treatment utilizing the active ingredient, comprising administering a therapeutically effective amount of a composition or solid oral dosage form according to the invention to provide pulsed or bimodal administration of the active ingredient.

[0029] Advantages of the present invention include reducing the dosing frequency required by conventional multiple IR dosage regimes while still maintaining the benefits derived from a pulsatile plasma profile. This reduced dosing frequency is particularly advantageous in the case of children in that it eliminates the need for dosing during the middle of the school day which can be both disruptive and embarrassing for the patient. It is also advantageous in terms of patient compliance to have a formulation which may be administered at reduced frequency. The reduction in dosage frequency made possible by utilizing the present invention would contribute to reducing health care costs by reducing the amount of time spent by health care workers on the administration of drugs. In the case of methylphenidate, and other controlled substances, the use of a once-daily formulation (in place of multiple IR doses) reduces or eliminates the need for the storage of controlled substances on the premises of schools or other institutions.

DESCRIPTION OF THE DRAWINGS

[0030] **FIG. 1** shows methylphenidate plasma profiles following oral administration of the following three formulations to human volunteers: A—20 mg methylphenidate formulation having an immediate release component comprising particles containing a total of 10 mg methylphenidate (according to Table 1 (ii)) and a modified release component comprising particles containing a total of 10 mg methylphenidate (according to Table 2 (viii); IR particles coated to a 30% weight gain);B—20 mg methylphenidate formulation having an immediate release component comprising particles containing a total 10 mg methylphenidate (according to Table 1 (ii)) and a modified release component comprising particles containing a total of 10 mg methylphenidate (according to Table 2 (vii); IR particles coated to a 30% weight gain); and Control—two doses of 10 mg Ritalin® Hydrochloride (IR) tablets administered at times 0

DETAILED DESCRIPTION OF THE INVENTION

[0031] The term "particulate" as used herein refers to a state, of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term "multiparticulate" as used herein means a plurality of discrete, or aggregated, particles, pellets, beads, granules or mixture thereof irrespective of their size, shape or morphology.

[0032] The term "modified release" as used herein in relation to the composition according to the invention or a coating or coating material or used in any other context means release which is not immediate release and is taken to encompass controlled release, sustained release and delayed release.

[0033] The term "time delay" as used herein refers to the duration of time between administration of the composition and the release of the active ingredient from a particular component.

[0034] The term "lag time" as used herein refers to the time between delivery of active ingredient from one component and the subsequent delivery of active ingredient from another component.

[0035] The invention will be described in detail with respect to methylphenidate as a specific example of an active ingredient particularly suited to formulation in a multiparticulate modified release composition according to the present invention.

[0036] The multiparticulate modified release composition of the invention may have more than two active ingredient-containing components. In this case the release of active ingredient from the second and subsequent components is modified such that there is a lag time between the release of active ingredient from the first component and each subsequent component. The number of pulses in the profile arising from such a composition in operation will depend on the number of active ingredient containing components in the composition. A composition containing three active ingredient-containing components will give rise to three pulses in the profile.

[0037] Any active ingredient for which it is useful to combine the advantages of a pulsatile plasma profile with a reduced frequency dosage regime may be used in practice of the present invention. Particularly useful in the practice of the invention include active ingredients whose pharmacological and/or therapeutic effects benefit from having a wash-out period between plasma concentration peaks, such as those active ingredients susceptible to the development of patient tolerance. Example active ingredients include but are not limited to peptides or proteins, hormones, analgesics, anti-migraine agents, anti-coagulant agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins and antidiuretic agents, drug compounds acting on the central nervous system such as cerebral stimulants, for example methylphenidate; pain management active ingredients; alkaloids such as opiates, for example morphine; cardiovascular drugs, such as nitrates; and agents for treating rheumatic conditions. It is further appreciated that the present inven-

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