IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN CORPORATION, PLC and ELAN PHARMA INTERNATIONAL LTD., Plaintiffs v. TEVA PHARMACEUTICALS USA, INC. Defendant.	Civil Action No. 07-552-SLR Hon. Sue L. Robinson

DEFENDANT'S RESPONSE TO PLAINTIFF'S MOTION TO DISMISS

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I. INTRODUCTION

Plaintiffs (collectively "Elan") have sued defendant Teva Pharmaceuticals USA, Inc. ("Teva") for infringement of two patents. Plaintiffs allege that Teva's filing of an Abbreviated New Drug Application ("ANDA") infringes the patents. Teva denies the alleged infringement, the validity of the patents, and the enforceability of the patents. Teva's affirmative defenses and counterclaims of unenforceability of the patents are based on alleged inequitable conduct committed by the patent applicants during their prosecution of the patents. Teva alleges that the patent applicants intentionally mischaracterized a prior art reference to deceive the Patent Office into issuing the patents. Elan moves to strike the inequitable conduct-related affirmative defenses and to dismiss the counterclaims for failure to state a claim.

Elan's motion should be denied. Elan's argument rests on the following erroneous legal proposition:

> As a matter of law, a patent applicant is permitted to mischaracterize a prior art reference before the Patent Office – with the intent to deceive the Patent Office – as long as the Patent Office has that prior art reference before it.

Elan's characterization of the law is flatly wrong – a patent applicant is not free to falsely characterize a prior art reference with intent to deceive the Patent Office. Elan cites no controlling case to support its argument. Indeed, if the law were as Elan would have this Court believe, patent applicants would be motivated to lie to the Patent Office to deceive the Patent Office into granting invalid patents. That would be antithetical to the uncompromising duty of candor that patent applicants owe to the Patent Office.

II. FACTUAL ALLEGATIONS

A. Background

The patents-in-suit, U.S. Patent Nos. 6,228,398 ("the '398 patent") and 6,730,325 ("the '325 patent"), generally relate to drug formulations comprising two populations of active drug particles, which are designed to be released at different times in a "pulsatile" manner. Some of the claims of the patents-in-suit relate specifically to a formulation of dexmethylphenidate, the active drug ingredient in Focalin XR®, a drug used to treat Attention Deficit Disorder.[1] The "XR" in Focalin XR® means "extended release." Teva seeks to make and sell a generic version of Focalin XR®, which has prompted this lawsuit.

Dexmethylphenidate is a controlled substance. In its immediate release form, sold as Focalin® or its generic version, the drug must be given multiple times daily. That means that school children taking the drug must often have a second daily dose of the drug administered at school by a teacher, who must keep the controlled drug in safekeeping, under lock and key, until the drug is taken by the child. The extended release formulations of the patents-in-suit deliver the drug into a patient's bloodstream in a "pulsatile" manner, meaning releasing the active drug in two phases, one soon after administration (like an immediate release formulation), the other hours later. Thus, the extended release "pulsatile" formulation of the patents-in-suit mimics the administration of two doses of immediate release formulations separated by several hours, eliminating the need for a patient, such as a school child, to have to take a second dose of drug during the school day.

[1] Dexmethylphenidate is one of two "isomers," mirror images of the same chemical structure, found in Ritalin®. *See* United States Patent No. 5,837,284, col. 1, l. 47 – col. 2, l. 12, *attached as* Exhibit A.

There is a prior art reference to the patents-in-suit that discloses the same formulation that is claimed in the patents-in-suit. In particular, U.S. Patent No. 5,837,284 to Mehta et al. ("the Mehta reference"), *attached as* Exhibit A,[2] discloses "a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit." Exh. A, col. 1, ll. 13-17. The Mehta reference discloses formulations designed to deliver time-delayed doses of medication into a patient's blood stream in a "pulsatile" manner. Like the patents-in-suit, the Mehta reference discloses an extended release "pulsatile" delivery formulation of dexmethylphenidate.

During prosecution of the patents-in-suit, the patent applicants characterized the Mehta reference as being distinguishable from their inventions. Their characterization of the Mehta reference is demonstrably false. Had the patent applicants characterized the Mehta reference accurately, the Patent Office would likely never had granted the patents-in-suit.

B. The Relevant Prosecution of the Patents-in-Suit

1. The '398 Patent

The patents applicants filed the application for the '398 patent on May 8, 2000. To persuade the Patent Office to examine its patent application on an accelerated basis, the patent applicants filed a document called a "Petition for Accelerated Examination" ("the Petition"). *See* Petition for Accelerated Examination, *attached as* Exhibit B. In conjunction with the Petition – and as required by Manual of Patent Examining

[2] The Mehta reference, the MPEP, as well as the prosecution history of the '398 patent, is part of the public record, and as such, can properly be considered while ruling on a motion to dismiss. *See Sands v. McCormick*, 502 F.3d 263, 268 (3rd Cir. 2007) ("[I]n ruling on a motion to dismiss, a district court relies on the complaint, attached exhibits, and matters of public record.").

Procedure ("MPEP"), Chapter 708.02, VIII(e)[3] – the applicants, through counsel, disclosed the prior art most closely related to the application; this included the Mehta reference. *Id.* The patent applicants were obligated to submit a detailed discussion of each reference explaining "how the claimed subject matter is patentable over the references." MPEP, Exh. C, Chapter 708.02, VIII(e).

In their discussion of the Mehta reference, the patent applicants implied that their invention was distinguishable from – and thus patentable over – the Mehta reference because the Mehta reference disclosed a formulation that was capable of a pulsatile release of drug only *in vitro* (i.e., in a test tube), not a formulation that yielded a pulsatile delivery *in vivo* (i.e., within the living body):

> U.S. Patent No. 5,837,284 (Mehta, *et al.)* is cited as categories A and P relevant to claims 1-36. Applicants would like to point out that the Mehta, *et al.* references discloses a formulation that is capable of a delayed release profile ***in vitro,*** but there is **not** disclosure of a formulation that produces an ***in vivo*** pulsed release profile.

Petition, Exh. B, at p. 2.

The patent applicants' characterization was demonstrably false. The Mehta reference discloses formulations capable of an *in vivo* pulsed release profile. In fact, there is a great deal of disclosure in the Mehta reference dealing with formulations to be administered to humans and their resulting *in vivo* pulsatile delivery of drug[4] – including

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[3] The MPEP codifies rules or regulations that must be followed before the Patent Office. They govern patent examiners, applicants, and their attorneys and agents. An excerpt of MPEP Chapter 708.02, VIII(e) is attached as Exhibit C.

[4] For example, the general description of the invention discloses "improved dosing of a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit," and "[t]he second, and any later, dose is time-delayed following administration," such that "the dosage forms can be formulated to deliver delayed doses ***in vivo*** at desired times." Mehta reference, Exh. A., col. 1, ll. 14-20 (emphasis added). The specification further provides the two releases "can be referred to as 'pulses,' and such a release profile can be referred to as 'pulsatile.'" *Id.*, col. 5, ll. 33-36.

a patent claim covering "[a] dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate[5] providing an *in vivo* plasma concentration of said d-threo-methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about 2 hours to about 7 hours, and wherein the magnitude of said maxima differ by no more than about 30 percent." Mehta reference, Exh. A., col. 16, ll. 47-53. It cannot be credibly disputed that the Mehta reference discloses formulations capable of an *in vivo* pulsed release profile.

2. The '325 Patent

Prior to the issuance of the '398 patent, the patent applicants filed a "continuation" of the application for the '398 patent. A "continuation" application is a second patent application containing the same disclosure as the original application, and claims priority to the same filing date, but includes different claims.[6] The patent applicants' continuation application consisted of the same specification as that of the '398 patent; only the claims differed. The Patent Office eventually allowed the claims of the continuation application to issue as the '325 patent.

Like the '398 patent, the Mehta reference discloses formulations that have each and every requirement of the claims of the '325 patent. However, at no point during the prosecution of the '325 patent did the patent applicants inform the Patent Office of their earlier false characterization of the Mehta reference, nor did they accurately characterize the Mehta reference.

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[5] d-threo methylphenidate or d-MPH is another way of referring to dexmethylphenidate.

[6] *See Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1579 (Fed. Cir. 1996) (Mayer, J., concurring) ("Although there may be some variation in the scope of the claimed subject matter, a continuation application is based solely on the disclosure of a parent application," and "[b]y definition, a continuation adds no new matter and is akin to an amendment of a pending application.") (citations omitted).

C. Teva's Pleading

On November 9, 2007, Teva filed its Answer and Counterclaims. Teva expressly pled that "during the prosecution of the '398 patent, those involved with the prosecution of the '398 patent and having a duty of candor to the Patent Office under 37 CFR 1.56, including the patent applications and their patent counsel, falsely and misleadingly characterized a piece of prior art before the Patent Office, with the intent to deceive the Patent Office in granting the '398 patent over the prior art reference." (Teva's Answer and Counterclaims p. 7, ¶14). The Answer and Counterclaims made direct reference to the June 2000 "Petition of Accelerated Examination," and quoted verbatim from that document, and the entirety of the applicant's mischaracterization of the Mehta reference. (*Id.* ¶¶15-17.) Teva further pled that the '325 patent is a continuation of the patent application that matured into the '398 patent, and that the inequitable conduct in prosecution of the '398 patent renders the '325 patent unenforceable under the doctrine of "infectious unenforceability" and "unclean hands." (*Id.* ¶¶24-25.)

Elan has not denied Teva's factual allegations or claim of inequitable conduct, either in its Reply to Teva's Counterclaims or in its papers in support of its motion to dismiss.

III. ARGUMENT

A. Teva's Inequitable Conduct Claim Relating To The '398 Patent States A Claim Upon Which Relief May Be Granted

1. Under 37 C.F.R. § 1.56 and Well-Settled Federal Circuit Authority, Teva Has Stated A Claim Of Inequitable Conduct

The factual allegations in a pleading must be taken as true for the purposes of a motion to dismiss on the pleadings. *See United States v. Ford Motor Co.*, 497 F.3d 1331, 1336 (Fed. Cir. 2007), citing *Gould, Inc. v. United States,* 935 F.2d 1271, 1274 (Fed. Cir.1991) ("In reviewing a motion to dismiss based on the pleadings, this court must accept all well-pleaded facts as true and view them in the light most favorable to the non-moving party."). Thus, it must be presumed in this motion that Teva's factual allegations are true, including that the patent applicants' characterization of the Mehta prior art reference was false, that the false characterization was material to patentability, and that the false characterization was made with the intent to deceive the Patent Office.[7] Accordingly, the sole issue before the Court is if Teva's pleading states a cognizable legal claim, i.e., can a patent applicant's intentional and material misrepresentation of a piece of prior art constitute inequitable conduct? The answer is yes.

All patent applicants owe the Patent Office a duty of candor. 37 C.F.R. § 1.56. The duty of candor is foundational to the U.S. patent system because the patent application process is an *ex parte* proceeding involving only the applicant and the Patent Office. The applicants' competitors and other members of the public are not privy to the

[7] As demonstrated previously, there is little doubt that the statements made in the Petition regarding the Mehta reference were false, in that the reference disclosed a formulation including dexmethylphenidate that produces an *in vivo* pulsed release profile plasma concentration. Evidence as to both the materiality and intent of that statement will be the focus of further inquiry during discovery.

proceedings and cannot serve as a check on representations made by the applicant to the Patent Office. Specifically, 37 C.F.R. § 1.56 states in relevant part:

> A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section.

37 C.F.R. § 1.56(a).

As the Rule states, the duty of candor includes the duty to submit all information known by the applicant to be material to patentability. "Material" information includes information that refutes or is inconsistent with a position taken by the applicant before the Patent Office or establishes by itself, or in combination with other information, a *prima facie* case of the unpatentability of the applicant's putative invention. 37 C.F.R. § 1.56(a).

The consequences of violating the duty of candor are severe. If the patent applicant, or anyone else having a duty of candor, has been found to have violated that duty with the intent to deceive the Patent Office, the patent is unenforceable. This is commonly known as "inequitable conduct." As the Court of Appeals for the Federal Circuit recently stated:

> Applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty. A breach of this duty-including affirmative misrepresentations of material facts, failure to disclose material information, or submission of false material information – coupled with an intent to deceive, constitutes inequitable conduct.

Nilssen v. Osram Sylvania, Inc., 504 F.3d 1223, 1229 (Fed. Cir. 2007), citing *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 999 (Fed. Cir. 2007). Thus, a

patent may be rendered unenforceable for inequitable conduct if an applicant, with intent to mislead or deceive the Patent Office, fails to disclose material information or submits materially false information to the Patent Office during prosecution. *Digital Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006), citing *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330-31 (Fed. Cir. 2004).

Teva has set forth in its pleading all of the requisite elements of inequitable conduct relative to the '398 patent. Teva pled that the patent applicants' characterization, through counsel, of the Mehta reference was false and even specifically identified their false statement. (Teva's Answer and Counterclaims, pp. 7, ¶¶15-16.) Teva pled that that the false statement was material to the patentability of the '398 patent and was made with the intent to deceive the Patent Office. (*Id.* at p. 8, ¶17.) Therefore, under Federal Circuit law, Teva has adequately pled inequitable conduct relative to the '398 patent.

2. District Courts Have Ruled That A Patent Applicant's Deliberate Mischaracterization Of A Prior Art Reference May Serve As The Basis For Inequitable Conduct

Consistent with Federal Circuit precedent, several district courts have ruled that a mischaracterization of prior art made to the Patent Office can support a claim of inequitable conduct. The case of *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 4 F. Supp. 2d 477 (E.D. Va. 1998) ("*SEL I*") is illustrative. There, the patentee was charged with committing inequitable conduct for deliberately mischaracterizing a prior art reference, the Tsai reference, to the Patent Office. *Id.* at 484-85. The court found that patentee's efforts to distinguish the Tsai reference before the Patent Office "were neither valid nor accurate" and that the patentee surely knew that its characterization of the Tsai reference was inaccurate. *Id.* at 485. Based on the finding that the patentee "knowingly

mischaracterized" the Tsai reference, the district court found that the patent was unenforceable. *Id.* at 485-86.

On a motion for reconsideration, the district court specifically rejected the very argument that Elan makes in this case – that a patent applicant's deliberately false characterization of prior art before the Patent Office cannot serve as the basis for inequitable conduct. *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 24 F. Supp. 2d 537, 542 (E.D. Va. 1998) ("*SEL II*"). Rejecting the patentee's interpretation of the Federal Circuit *Akzo* case – the same interpretation offered by Elan here – the district court in *SEL II* stated that *Akzo* stands for the proposition that when neither a proved material misrepresentation nor a proved intent to deceive the Patent Office exists, inequitable conduct has not been proven. *Id.* at 542, citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471 (Fed. Cir. 1986). The court in *SEL II* aptly noted that, by implication from *Akzo*, where a material misrepresentation with the intent to deceive ***has*** been proven, as in the *SEL* litigation and as pled by Teva in this case, inequitable conduct ***does*** exist. *Id.* at 542. Under the *SEL* cases, and the *SEL II* court's interpretation of *Akzo*, Teva has made out a claim of inequitable conduct.

The holding in *SEL* is consistent with the application of the law of inequitable conduct by this district. *See eSpeed, Inc. v. Brokertec USA, LLC*, 417 F. Supp. 2d 580 (D. Del. 2006); *Mobil Oil Corp. v. Advanced Environmental Recycling Technologies, Inc.*, 869 F. Supp. 251 (D. Del. 1994), *aff'd* 92 F.3d 1203 (Fed. Cir. 1996). In *eSpeed, Inc.*, for example, the issue of alleged inequitable conduct was tried to Judge Jordan. During the prosecution of the application of the patent-in-suit, several patent applicants provided declarations to the Patent Office about a piece of prior art. *eSpeed, Inc.*, 417 F.

Supp. 2d at 590. The patent applicants asserted that the prior art did not contain a new version of computer code material to the patentability of the invention, and, instead, contained a prior version of code. *Id.* However, the underlying prior art attached to the declarations demonstrated that the reference, in fact, contained the new version – thus, directly contradicting the patent applicants' declarations. *Id.* at 598. In finding that the patentee committed inequitable conduct, Judge Jordan stated that, "[m]ischaracterizing a reference in a way that misleads the PTO has been found to amount to inequitable conduct." *Id.* Judge Jordan found that the patentee's conduct constituted inequitable conduct because, "[t]he applicants misleadingly indicated that the [prior art] did not contain new rules, while submitting documentation that showed the contrary."[8] *Id.* at 598-99.

Other district courts are in accord with Judge Jordan's ruling. *See, e.g., Transocean Offshore Deepwater Drilling, Inc. v. Globalsantafe Corp.*, 2006 U.S. Dist. LEXIS 57967 (S.D. Tex. August 17, 2006) (finding that factual assertions concerning prior art before the Patent Office was capable of supporting a claim for inequitable conduct). Thus, contrary to Elan's arguments, false and misleading representations regarding the content of a prior art reference may constitute inequitable conduct, even when the underlying prior art has been cited to the Patent Office.

3. A Misrepresentation Made In A Petition To Make Special Is Material *Per Se* And Independently Supports A Finding Of Inequitable Conduct.

Not only can a knowingly false or misleading mischaracterization of prior art constitute inequitable conduct, but when made in the context of a Petition to Make

[8] While Elan's counsel cited other, unpublished Delaware cases in Elan's brief, Elan's counsel failed to cite the *eSpeed* case in its brief. Elan's lead counsel is undoubtedly aware of *eSpeed*, as he represented the patentee in *eSpeed*.

Special, those statements can also independently support a finding of inequitable conduct. *See General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405, 1411 (Fed. Cir. 1994) ("We conclude as a matter of law that a false statement in a petition to make special is material if, as in the case here, it succeeds in prompting expedited consideration of the application."); *Scanner Techs. Corp. v. ICOS Vision Sys. Corp., N.V.*, 486 F. Supp. 2d 330, 345-47 (S.D.N.Y. 2007) ("Intentionally making a false or misleading statement in a Petition to Make Special is inequitable conduct and renders a resulting patent unenforceable"); *GFI Inc. v. Franklin Corp.*, 88 F. Supp. 2d 619, 632 n.17 (N.D. Miss. 2000) ("Misleading statements in a Petition to Make Special can independently form the basis of a finding of inequitable conduct.").

Statements in a Petition to Make Special are afforded special consideration because, in exchange for having his patent application examined on an accelerated basis, the applicant has assumed an affirmative duty to assist the Patent Office in finding and parsing the prior art. In fact, one of the requirements for receiving a granted petition is that the applicant must submit "a detailed discussion of the references, which discussion points out, with the particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is patentable over the references." MPEP, Exh. C, Chapter 708.02, VIII(e). The Patent Office is entitled to rely on the truthfulness of the representations in the patent applicant's petition:

> [t]he whole point of the PTO requirement that a petition to make special include a sworn statement that the applicant has made a careful and thorough search is that, in return for an applicant being put at the head of the examining line, he must make an extra effort to look for and produce all relevant prior art, in other words, ***to assist an examiner who is being asked to expedite examination***.

General Electro Music Corp., 19 F.3d at 1411 (emphasis added).

Further, the information in the petition is deemed material to patentability ***per se***. As the Federal Circuit has stated, "[b]y filing a petition to make special, [the applicant] thus requested special treatment and induced reliance on its statement" regarding the scope and breadth of the prior art, and that the applicant "cannot now argue that the statement was immaterial." *Id.*

Thus, while the Elan patent applicants were supposed to be assisting the Patent Office with a complete and truthful characterization of the prior art listed in their Petition to Make Special, they completely mischaracterized the Mehta reference in such a false way that, if believed and relied on by the Patent Office, would have led to the issuance of an invalid patent. The false mischaracterization of the Mehta reference was *per se* material to the patentability of the patents-in-suit. Teva's allegations of inequitable conduct undeniably state a claim for inequitable conduct.

4. There Is No Federal Circuit Authority Supporting Elan's Argument, And The Few District Court Cases On Which Elan Relies Are Inapposite

a. There Is No Federal Circuit Law Standing For The Proposition That A Patent Applicant Is Free To Deliberately Mischaracterize Prior Art To The Patent Office To Deceive The Patent Office

Elan implies that there is Federal Circuit authority for the proposition that a patent applicant's deliberate mischaracterization of a prior art reference to the Patent Office cannot serve as the basis for inequitable conduct as long as the prior art was before the Patent Office. There is no such authority.

Elan relies on the Federal Circuit *Azko N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471 (Fed. Cir. 1986) case, the case distinguished in *SEL II*, as described above. *Akzo* was an appeal of an International Trade Commission decision, among other things,

affirming an ITC finding that the patentee had not committed inequitable conduct. The appellants argued that the patentee committed inequitable conduct by submitting an affidavit to overcome the Patent Office's obviousness rejections that failed to compare the patented invention with the closest prior art, and by arguing that two prior art references did not anticipate the invention. *Id.* at 1481. The ITC found that the patentee had not made material misrepresentations in its affidavit or arguments to the Patent Office, and that it was instead merely distinguishing its invention from the prior art. *Id.* at 1482. As the district court in *SEL II* held, as explained above, *Akzo* thus does not stand for the broad proposition for which Elan has cited it, namely, that a patent applicant is free to deliberately falsely mischaracterize prior art before the Patent Office with the intent to deceive the Patent Office. *See, SEL II*, at 542.

The case of *Young v. Lumenis, Inc.*, 492 F.3d 1336 (Fed. Cir. 2007) is also off point. In *Young*, the defendant charged the patentee with inequitable conduct for withholding material information from the Patent Office and mischaracterizing prior art. *Id.* at 1347. The district court granted summary judgment that the patentee committed inequitable conduct. *Id.* at 1348. The Federal Circuit reversed, find that there was no withholding of material information and no mischaracterization of prior art. *Id.* at 1350. As to the alleged mischaracterizations, the Federal Circuit stated that they were "attorney argument, attempting to distinguish the claims [of the patent-in-suit] from the prior art, not gross mischaracterizations or unreasonable interpretations of the [prior art]." *Id.* at 1349. Thus, Young merely stands for the proposition that the defendant advancing an inequitable conduct defense must prove a material misrepresentation as an element to proving inequitable conduct. As Teva will prove at trial (and as already demonstrated in

the facts section of this brief), Elan's patent applicants' characterization of the prior art Mehta reference was not only a "gross mischaracterization," but it was flatly untrue. For the sake of this motion, however, it suffices that Teva has pled that Elan's patent applicants falsely characterized the Mehta reference.

The case of *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320 (Fed. Cir. 2000) is similarly inapposite. In *Life Techs.*, the Federal Circuit reversed a district court's finding after a bench trial that the patentee had committed inequitable conduct for, among other things, mischaracterizing a prior art reference. *Id.* at 1327. The Federal Circuit ruled that the district court's fact finding was clearly erroneous, on the grounds that the patentee did not make a misrepresentation. *Id.* at 1326. The Elan patent applicants did make a misrepresentation in this case, and Teva has pled the specific misrepresentation.

Elan's reliance on the other Federal Circuit cases it cites is similarly misplaced, as those cases involved an allegation of the withholding of prior art, not the deliberate mischaracterization of it. *See Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318 (Fed. Cir. 2000); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172 (Fed. Cir. 1995). In *Fiskars*, the defendant charged the patentee with inequitable conduct for withholding several prior art references from the Patent Office. *Id.* at 1326. The district court found, as a matter of fact, that the patentee had not withheld the prior art from the Patent Office. *Id.* at 1327. The district court therefore ruled that the patentee had not committed inequitable conduct. *Id.* The Federal Circuit affirmed, noting that "[a]n applicant is not required to tell the PTO twice about the same prior art." *Id.* Thus, Elan's cropped quote from *Fiskars* that "[a]n applicant can not be guilty of inequitable conduct if the reference was cited to the

examiner, whether or not it was a ground of rejection by the examiner" – for the proposition that a deliberate mischaracterization of prior art cannot constitute inequitable conduct – is misleading, because the allegation of a deliberate mischaracterization of prior art was never at issue in *Fiskars*.[9]

b. The District Court Cases Cited By Elan, Some Unpublished, Are Similarly Inapposite Or Contain *Dicta* Misconstruing Federal Circuit Precedent

Elan cites a handful of district court cases in arguing that a patent applicant is free to deliberately mischaracterize prior art to the Patent Office. Those cases do not stand for such a proposition.

For example, the case of *Bayer AG v. Dr. Reddy's Labs., Ltd.*, 2007 WL 3120794, __ F. Supp. 2d __, (D. Del. October 25, 2007), issued by this Court, did not even involve an allegation of a deliberate mischaracterization of prior art. *Bayer AG*, 2007 WL 3120794, at __ ("Reddy alleges that the applicants committed inequitable conduct before the PTO by failing to properly disclose four references during the prosecution of the '434 application.")[10]

In *Blackhawk Molding Co., Inc. v. Portola Packaging, Inc.*, 422 F. Supp. 2d 948 (N.D. Ill. 2006), the district court granted summary judgment of no inequitable conduct because the defendant failed to establish any fact issue as to whether the alleged

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[9] The relevance of Elan's citation to *Molins* is unclear, as Elan has not explained its citation of this case, and again, there was no misleading mischaracterization of prior art at issue in that case. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1884 (Fed. Cir. 1995) ("Here, the reference was not mischaracterized, but it was submitted along with a multitude of references.").

[10] Thus, Elan's cropped quote, "[W]here all the pertinent information was available to the examiner, the defendant's inequitable conduct defense may fail as a matter of law for lack of materiality" is misleading because the court did not address the issue of a deliberate mischaracterization of the prior art.

misrepresentations at issue were false or material. *Id.* at 963. The case does not stand for the proposition that a false characterization of a prior art reference made to deceive the Patent Office cannot constitute inequitable conduct.

The case of *Bayer Healthcare LLC v. Abbott Labs.*, 2004 WL 2862267 (D. Del. De. 10, 2004) from this district is irrelevant, because the inequitable conduct allegation in that case involved the alleged mischaracterization of certain claims in the patentee's patent application. *Id.* at *4-*5. There, Judge Sleet granted the patentee's motion for summary judgment that no inequitable conduct had occurred on the grounds that the Patent Office is presumed to be able to read and understand the claims of a patent application. *Id.* at *7. The case did not involve an allegation of the deliberately false characterization of prior art, so it has no applicability to the present motion.[11]

Finally, there are the cases of *Semiconductor Energy Lab. Co. Ltd. v. Chi Mei Optoelectronics Corp.*, 2007 WL 1793770 (N.D. Cal. June 19, 2007), *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 2004 WL 2239248 (D. Del. Sept. 27, 2004), and *Lifescan, Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 379 (D. Del. 2000). In *Semiconductor Energy Lab. Co.*, an unpublished case, the district court granted summary judgment of no inequitable conduct to the patentee on the issue of alleged mischaracterization of a prior art reference, citing *Akzo* for the proposition that, because the Patent Office had the reference, the patentee could not have committed inequitable conduct regardless how the patentee characterized the reference. *See Semiconductor Energy Lab. Co.*, 2007 WL 1793770 at *8. However, it is clear that the district court's reliance on *Akzo* was wrong,

[11] The only applicability to Elan's motion this case may have is that the district court specifically granted the defendant leave to amend its pleadings to assert its inequitable conduct theory. *Id.* at *1-2.

because Akzo involved an alleged withholding of prior art, not a mischaracterization of it. The *Semiconductor Energy Lab.* court simply misapplied *Akzo*.

The same misapplication of *Akzo* was made by Judge Sleet of this district in the unpublished case of *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 2004 WL 2239248 (D. Del. Sept. 27, 2004). In that case, the defendant filed a motion for attorney's fees, claiming that the patent infringement suit filed against it qualified as an "exceptional case" under 35 U.S.C. § 285.[12] One of the arguments the defendant advanced in support of its motion was that the patentee committed inequitable conduct during patent prosecution by mischaracterizing a prior art article. *Id.* at *1. Judge Sleet denied the motion, relying on *Semiconductor Energy Lab. Co. v. Samsung Electronics Co.*, 204 F.3d 1368, 1377 (Fed. Cir. 2000), apparently for the proposition that inequitable conduct could exist only where "the examiner only had an incomplete summary of the prior art or a partial translation of prior art written in another language." *Genzyme Corp.*, 2004 WL 2239248 at *2. However, like *Akzo*, *Semiconductor Energy Lab* was a case in which the claimed inequitable conduct was based on the alleged withholding of prior art, not on a deliberate false characterization of it. *See Semiconductor Energy Lab. Co. v. Samsung Elec. Co.*, 204 F.3d 1368 (Fed. Cir. 2000) ("Thus, SEL deliberately deceived the examiner into thinking that the Canon reference was less relevant than it really was, and constructively withheld the reference from the PTO," and "SEL's submission hardly satisfies the duty of candor required of every applicant before the PTO"). *Semiconductor*

[12] Section 285 permits a party to seek attorney's fees in "exceptional cases." The Federal Circuit has noted that "exceptional cases" occur where the asserting party proves by clear and convincing evidence that there was "inequitable conduct before the PTO; litigation misconduct; vexatious, unjustified, and otherwise bad faith litigation; a frivolous suit or willful infringement." *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1034 (Fed. Cir. 2002), citing *Hoffmann-La Roche Inc. v. Invamed Inc.*, 213 F.3d 1359, 1365 (Fed. Cir. 2000).

Energy Lab does not hold that a patent applicant is free to deliberately mischaracterize prior art to deceive the Patent Office. Thus, the rationale of the unpublished *Genzyme* decision does not apply here.

Finally, in *Lifescan, Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 379 (D. Del. 2000), Judge Sleet ruled after a bench trial on the issue that the patentee had not committed inequitable conduct by its characterization of prior art patents in an Information Disclosure Statement.[13] *Id.* at 385-86. The court found that the patentee's characterization of the prior art, as a matter of fact, was neither false nor misleading. *Id.* at 386. Judge Sleet went on to state in *dicta* that, even if the patentee's characterization of the prior art had been inaccurate; the mischaracterization would not rise to the level of a material misrepresentation. *Id.* at 386. Judge Sleet, citing *Akzo*, reasoned that the Federal Circuit had previously recognized that, "the mere fact that a patent applicant attempts to distinguish its patent from the prior art does not constitute a material omission or misrepresentation where the patent examiner has the prior art before him or her, and therefore, is free to make his or her own conclusions regarding the claimed invention." *Id.* However, as described previously, *Akzo* merely stands for the proposition that when neither a proved material misrepresentation nor a proved intent to deceive the Patent Office exists, inequitable conduct has not been proven.[14] *See SEL II.* at 542, citing *Akzo N.V.*, 808 F.2d at 1482.

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[13] An Information Disclosure Statement is a document filed with the Patent Office during the prosecution of a patent application which provides the patent examiner with patents, publications, or other information that the patent applicant believes the examiner should consider in determining the patentability of the claimed invention. *See* 37 C.F.R. §§ 1.97 and 1.98.

[14] The *Lifescan* court also cited, in passing, *Gargoyles Inc. v. U.S.*, 32 Fed. Cl. 157 (Fed. Cl. Ct. 1994). However, in that case, the court merely found that, after a five-day trial, that the party asserting inequitable conduct failed to demonstrate, by clear and convincing evidence, that the patent applicant's interpretation of a prior art reference was demonstrably erroneous; that it knew

B. Teva's Inequitable Conduct Claim Relative To The '325 Patent States A Claim Upon Which Relief May Be Granted

Teva counterclaimed that Elan's '325 patent was unenforceable due to inequitable conduct based on the doctrine of "infectious unenforceability" or "unclean hands."[15] (Teva's Answer and Counterclaims, at p. 8, ¶¶ 24-25.) This doctrine renders patents that issue from applications related to another patent application that involved inequitable conduct (e.g., the application that matured into the '398 patent) unenforceable. It is premised on the Federal Circuit's longtime principle that "the duty of candor extends through the patent's entire prosecution history," and that a breach of the duty of candor "may render unenforceable all claims which eventually issue from the same ***or a related application.***" *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 24 F. Supp. 2d 537, 543 (E.D. Va. 1998) (quoting *Fox Industries, Inc.*, 922 F.2d at 803-04) (emphasis in original).

"[A] patent that issues from a divisional or continuation application may be held unenforceable where (i) there is inequitable conduct with respect to the prosecution of an earlier related application in the chain leading to the challenged patent and (ii) the inequitable conduct relates to the asserted claims of that patent." *Id.* at 543-44. "Inequitable conduct earlier in a chain of related patent applications must be cured . . . or it will continue to infect the process; cure cannot be achieved through manipulation of

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its interpretation was erroneous; or that it intended to deceive the Patent Office. *Id.* at 169. For purposes of this motion, such findings must be presumed in Teva's favor, and accordingly, this case is inapposite.

[15] As to Elan's footnote concerning the pleading of unclean hands, we note that where the claim is "is an incorporation of the allegations supporting [the] inequitable conduct claim . . . the unclean hands defense will stand or fall with the inequitable conduct claim." *Collaboration Properties, Inc. v. Tandberg ASA*, 2007 WL 205065, at *7 (N.D. Cal. January 5, 2007).

patent prosecution procedures, such as canceling or amending claims or filing continuation and divisional applications." *Id.* at 544-45.

Teva alleges in its Answer and Counterclaims that the '325 patent, which is based on a continuation application of the '398 patent, is unenforceable as a result of the material false and misleading statements the applications submitted to the PTO – with intent to deceive – during the prosecution of the parent patent application (i.e., the patent application that matured into the '398 patent). This is a properly pled claim of inequitable conduct relative to the '325 patent. Accordingly, Elan's motion as to the inequitable conduct pleading relating to the '325 patent should be denied.

III. CONCLUSION

For all of the foregoing reasons, Teva respectfully requests that Elan's motion be denied.

Dated: December 17, 2007

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN CORPORATION PLC and ELAN PHARMA INTERNATIONAL LTD., Plaintiffs, vs. TEVA PHARMACEUTICALS USA, INC., Defendant.	C.A. NO. 07-552-SLR

DECLARATION OF SAMUEL T. LOCKNER

I, Samuel T. Lockner, hereby declare as follows:

1. I am counsel of record for Defendant Teva Pharmaceuticals USA, Inc., (Teva) in the above-captioned matter.

2. Attached hereto as Exhibit A is a true and correct copy of United States Patent 5,837,284 ("the Mehta reference").

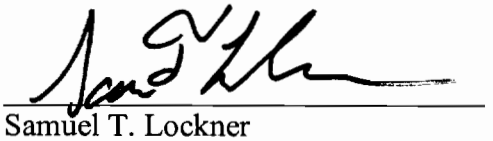
3. Attached hereto as Exhibit B is a true and correct copy of the Petition for Accelerated Examination dated June 8, 2000, from Patent Application of John Devane et al., Serial No. 09/566,636.

4. Attached hereto as Exhibit C is a true and correct copy of Chapter 708.02 from the Manual of Patent Examining Procedure ("MPEP").

I declare under penalty of perjury under the laws of the United States of America that the

foregoing is true and correct.

Executed on December 17, 2007.



Samuel T. Lockner

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**

[76] Inventors: **Atul M. Mehta**, 252 E. Cresent Ave., Ramsey, N.J. 07446; **Andrew L. Zeitlin**, 1500 Whitebridge Rd., Millington, N.J. 07946; **Maghsoud M. Dariani**, 11 Byron La., Fanwood, N.J. 07023

[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

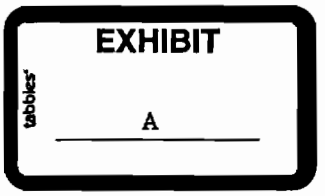
PDR, 46th ed. "Ritalin SR" pp. 880–881, 1992.

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

[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



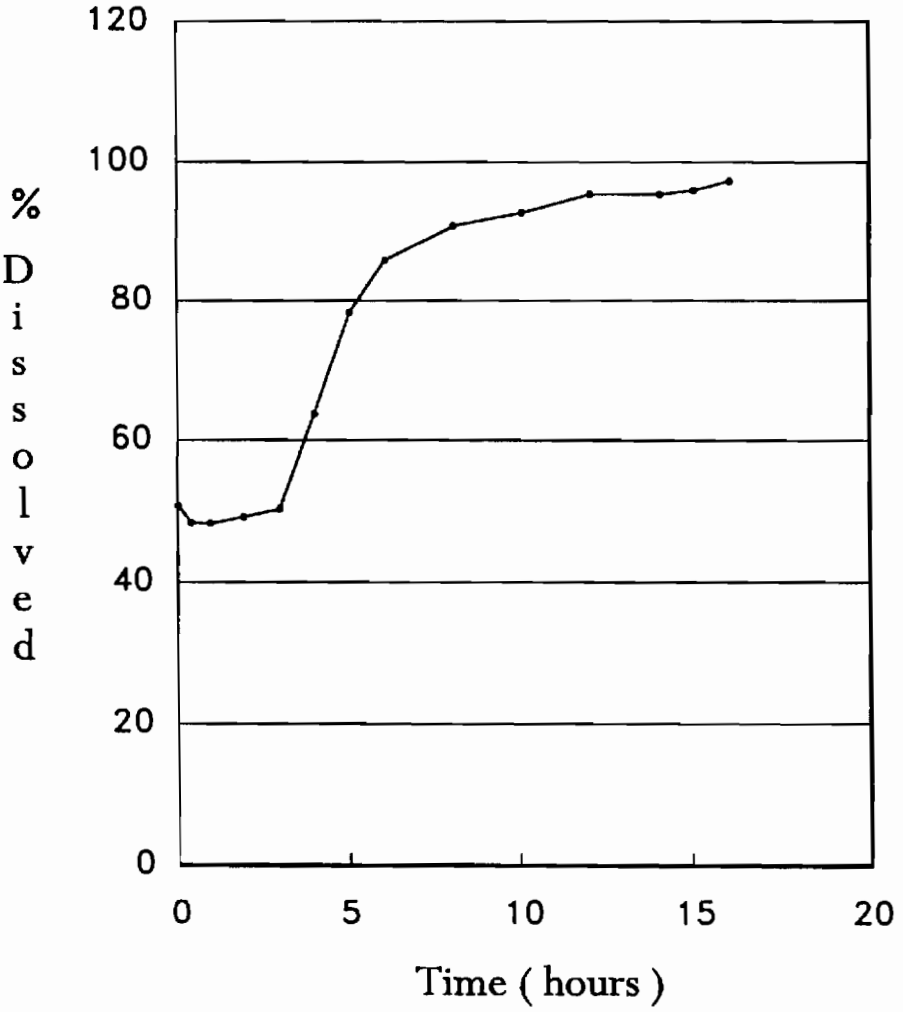


FIG. 1

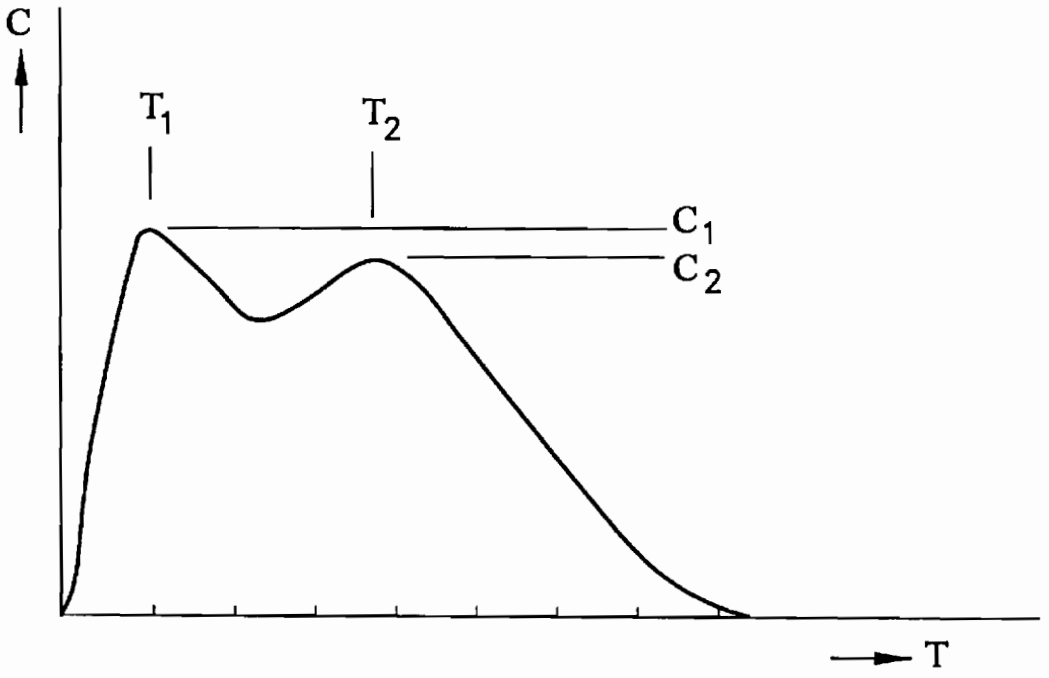


FIG. 2

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.

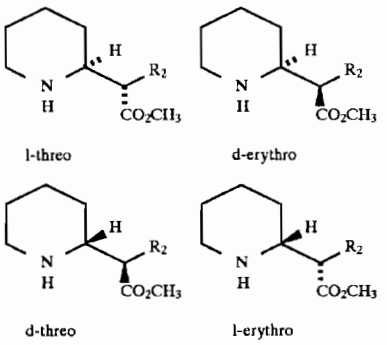
The dosage forms and methods of the present invention are particularly suitable for the administration of methylphenidate hydrochloride, and especially for the administration of a single isomer, d-threo-methylphenidate hydrochloride.

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:



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-

for substantially immediate release of the drug once the dosage form is ingested by a patient. Such forms include, for example, powders, coated and uncoated pellets, and coated and uncoated tablets. The dose for immediate release can be administered in a tablet or capsule form which may also include the delayed dose. For example, two or more groups of pellets may be combined within a hard gelatin capsule or compressed into a tablet. Powders can be granulated and can be combined with pellets and excipients and/or other additives, and contained within a capsule or compressed into a tablet. These and other dosage forms will be familiar to those skilled in the art.

The delayed dose of a methylphenidate drug in the dosage forms of the present invention is provided in part by the use of certain copolymers referred to as "ammonio methacrylate copolymers". Ammonio methacrylate copolymers comprise acrylic and/or methacrylic ester groups together with quaternary ammonium groups. According to the present invention, the copolymers are incorporated into a formulation which is used to coat particles containing a medication.

The "acrylic and/or methacrylic ester groups" in the copolymers used in the compositions and methods of the present invention are referred to herein collectively as "acrylic groups". The acrylic groups are preferably derived from monomers selected from C_1–C_6 alkyl esters of acrylic acid and C_1–C_6 alkyl esters of methacrylic acid. Preferred are C_1–C_4 alkyl esters of acrylic acid and methacrylic acid. Suitable monomers include, for example, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate. Ethyl acrylate and methyl methacrylate are preferred, and copolymers containing ethyl acrylate and methyl methacrylate are highly preferred. Also preferably, the copolymers have a molecular weight of about 150,000.

Quaternary ammonium groups in copolymers useful in forming coatings for use in the dosage forms of the present invention can be derived from monomers comprising quaternary ammonium groups. Preferably, the monomers are alkyl esters of acrylic or methacrylic acid, comprising alkyl groups having from 1 to 6 carbon atoms and a quaternary ammonium group in the alkyl portion. Monomers comprising quaternary ammonium groups can be prepared, for example, by reaction of monomers containing amino groups with alkylating agents such as, for example, alkyl halides, especially methyl chloride. Suitable monomers containing amino groups include 2-(N,N-dibutylamino)ethyl acrylate, 2-(N,N-dibutylamino)ethyl methacrylate, 4-diethylamino-1-methyl-butyl acrylamide, and 4-diethylamino-1-methyl-butyl methacrylamide. Other useful monomers containing amino groups are disclosed in U.S. Pat. No. 5,422,121, the disclosure of which is incorporated herein by reference. Particularly preferred as a monomer comprising a quaternary ammonium group is trimethylammonioethyl methacrylate chloride (TAMCl).

While ammonio methacrylate copolymers such as those described herein have been used for sustained delivery of certain medicaments, i.e., for the relatively constant administration of a drug, it has been surprisingly and unexpectedly found that dosage forms comprising a methylphenidate drug and a coating prepared from one or more ammonio methacrylate copolymers and certain fillers, can provide delayed or pulsatile release of the drug, a very distinct phenomenon. Methylphenidate drugs are amine-containing, rely upon body or membrane loading for efficacy, and are psychotropic. The ability to provide delayed release of a methylphenidate drugs using ammonio methacrylate copolymers is due to a combination of factors, including the composition of the ammonio methacrylate copolymers used, and the amount and composition of filler.

The ratio of acrylic groups to quaternary ammonium groups in the ammonio methacrylate copolymers influences the properties of the copolymers utilized in forming the coatings of the present invention. For use in the dosage forms and methods of the present invention, the ratio of acrylic groups to quaternary ammonium groups in the copolymers is preferably from about 10:1 to about 50:1, more preferably from about 15:1 to about 45:1. Preferably, in preparing a dosage form according to the present invention, two or more copolymers are used in combination. Also preferably, one of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 25:1 to about 45:1, more preferably from about 30:1 to about 40:1, and another of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 25:1, more preferably from about 15:1 to about 20:1. Even more preferably, two ammonio methacrylate copolymers are used: a first copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 30:1 to about 40:1 and the second copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 15:1 to about 20:1. Most preferably, the copolymers are copolymers of methyl methacrylate, ethyl acrylate, and TAMCl, in ratios of 2:1:0.1 for the first copolymer and 2:1:0.2 for the second copolymer.

When two such ammonio methacrylate copolymers are used to form the coatings, the relative amounts of the two polymers is partly determinative of the delay and release properties of the dosage forms of the present invention. It is preferred that the ratio between the first polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 30:1 to about 40:1, and the second polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 15:1 to about 20:1, be from about 93:7 to about 97:3. More preferably, the ratio of the first polymer to the second polymer is from about 96:4 to about 94:6, and most preferably about 95:5.

Ammonio methacrylate copolymers used in the coatings of the dosage forms of the present invention can be prepared by methods known to those skilled in the art. Exemplary methods include emulsion polymerization, bulk polymerization and suspension polymerization. A suitable procedure is described in U.S. Pat. No. 3,979,349, the disclosure of which is incorporated herein by reference. Suitable ammonio methacrylate copolymers are known per se, and can be purchased from commercial providers. For example, suitable ammonio methacrylate polymers are available from Hüls America under the Eudragit® trademarks. The Eudragit® polymers and similar polymers, including methods for preparation, are described in Klaus O. R. Lehman, "Chemistry and Application Properties of Polymethacrylate Coating Systems", *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd. Ed., pp. 101–174, James Mc Ginity, Ed., Marcel Dekker, Inc., New York (1996), the disclosure of which is incorporated herein by reference.

The coatings of the present invention also preferably include a filler. The filler is preferably in powder form and is preferably hydrophobic. Exemplary fillers include talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate. Talc is a particularly preferred filler.

The quantity of filler used in preparing coatings for the dosage forms of the present invention should be sufficient to minimize agglomeration of the particles. Agglomeration is highly undesirable because the agglomerates, rather than discrete particles, will become coated. Agglomerates are

tic effectiveness and minimize undesirable side effects. In certain preferred embodiments, the dosage forms of the present invention provide administration of the two threo forms of methylphenidate. In particularly preferred embodiments, the dosage forms of the present invention provide administration of a single isomer, d-threo-methylphenidate, albeit in two or more doses.

The dosage forms of the present invention are intended for oral ingestion by a mammal, particularly a human. The dosage forms of the present invention are particularly suitable for the administration of methylphenidate drugs, in at least two doses. Most preferably, the dosage forms provide two doses of a d-threo methylphenidate drug such as d-threo methylphenidate hydrochloride. The second dose can be delayed by from about 2 hours to about 7 hours, preferably from about 3 hours to about 6 hours, and most preferably from about 4 hours to about 5 hours, following ingestion of the dosage form by a mammal. This eliminates the need for a patient, for example a child being treated for ADD, to carry a second dose for ingestion several hours after ingestion of a first dose. The exclusion of the l isomers and the d-erythro isomer eliminates the concurrent ingestion of forms of methylphenidate principally believed to be associated with adverse side effects and/or reduced effectiveness.

The temporal separation of the two doses provided according to the present invention can be represented graphically as in FIG. 1. FIG. 1 is an in vitro drug release profile of a dosage form of the present invention. The data were obtained by measuring the rate of dissolution of drug as a function of time. In this embodiment two doses are provided. The release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration. Following a period of little or substantially no drug release, the second dose is released. The two releases can be referred to as "pulses", and such a release profile can be referred to as "pulsatile".

FIG. 2 is a schematic representation of the plasma concentration of drug resulting from a release profile according to FIG. 1. The maximum concentration due to the first dose, C_1, occurs at t_1, preferably from about 1 hour to about 3 hours after ingestion, most preferably about 2 hours after ingestion. The release of the first dose is followed by a period during which substantially no drug is released, which lasts approximately 2–6 hours, preferably 3–5 hours, post ingestion. The second dose is then released, with the maximum concentration, C_2, at t_2, which is preferably about 6 hours post-ingestion. Preferably at least about 80% of the total drug has been released by about 6 hours following administration. In the embodiment represented by FIG. 2, the levels of drug released at the two maxima are nearly equal. Preferably, if two approximately equal doses are released, the release of the two doses provides a plasma concentration profile having two maxima, which differ from each other by no more than about 40 percent in magnitude, preferably by no more than about 30 percent, and more preferably by no more than about 25 percent. This is determined by the relationship:

$$|C_1-C_2|/C_1$$

In such embodiments is most preferred that the maxima differ by no more than 20%. However, embodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art.

Dosage forms of the present invention provide controlled release of a methylphenidate drug, including pharmaceutically acceptable salts of methylphenidate, whereby an initial dose for immediate release can be combined with a delayed release of one or more additional doses. Such dosage forms may alternatively be referred to as "pulsatile" dosage forms.

"Immediate release", as used herein, means release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion. "Delayed release", as used herein, refers to a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released. The terms "medication" and "drug" are used interchangeably herein.

According to the present invention, delayed release dosage forms can be combined with forms which provide immediate release of a drug. Thus, two or more dosage forms can be combined, one dosage form providing a portion of a patient's daily dosage needs of a drug and subsequent dosage forms providing additional portions of a patient's daily dosage needs. For example, a drug can be administered to a patient in two dosage forms simultaneously, one providing, e.g., about 30–50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement. Alternatively, and preferably, a single dosage form can be administered which includes an immediate dose of some portion of a patient's daily requirement and one or more delayed doses to provide the remaining portion or portions of the patient's daily requirement.

Dosage forms of the present invention provide an initial dose of a drug such as, for example, a pharmaceutically acceptable salt of d-threo-methylphenidate (also referred to herein as d-MPD), followed by an interval wherein substantially no additional drug is released, followed in turn by release of a second dose. If desired, a second substantially release-free interval may be provided following the second release, followed in turn by a third dose. Thus, dosage forms providing 3 or more doses are contemplated by the present invention. However, dosage forms providing 2 or 3 doses are generally preferred for therapeutic use, with 2 doses being more preferred. For example, the first dose can provide from about 30 percent to about 70 percent of a patient's daily prescribed intake of the drug and the second dose provides from about 70 percent to about 30 percent. If two approximately equal doses are desired, the initial dose preferably provides from about 40 percent to about 60 percent, and the second dose preferably provides from about 60 percent to about 40 percent, of a patient's prescribed daily intake of the drug. If desired, the first dose and the second dose can each provide about 50 percent of a patient's prescribed daily intake of drug. However, as will be apparent to one skilled in the art, the effect of drug metabolism in the body may require adjustment of the relative amounts of each dose, so that, for example, the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism. This can be observed in FIG. 2, which, as discussed above, represents the blood plasma level of a drug, such as a methylphenidate drug, delivered in a dosage form which provides a release profile as illustrated in FIG. 1.

The initial dose of methylphenidate drug in the dosage forms of the present invention can be provided by incorporating the methylphenidate drug into a form which allows

susceptible to breaking into discrete particles, which will be partially uncoated, resulting in unwanted variability in release rates. Preferably, the amount of filler is from about 30 percent to about 50 percent by weight, based on the total weight of the dry polymer, commonly referred to as "total solids". More preferably the amount of filler is from about 35 percent to about 45 percent of total solids, and most preferably about 40 percent.

Coatings used in the dosage forms of the present invention also preferably include a material which improves the processing of the copolymers. Such materials are generally referred to as "plasticizers" and include, for example, citric acid esters, adipates, azelates, benzoates, citrates, stearates, isoebucates, sebacates, propanetriol acetate, polyethylene glycols, diethyl phthalate, dibutyl sebacate, propylene glycol and ethylene glycol. Citric acid esters are preferred, and triethyl citrate is particularly preferred. The amount of plasticizer to be used in the coating is preferably from about 10 percent to about 30 percent, more preferably from about 15 percent to about 25 percent, and most preferably about 20 percent, based on the weight of the dry polymer, i.e., total solids.

Dosage forms of the present invention preferably comprise particles containing d-MPD. In one embodiment, the dosage form comprises two groups of particles. A first group of particles provides the initial dose of d-MPD. As stated hereinabove, the initial dose can be in powder, pellet or other particulate form and can be uncoated. If the initial dose is in the form of a powder or sufficiently small particles, it can, if desired, be pressed into a solid form such as a tablet or caplet. In this embodiment, the delayed dose is provided by a second group of particles. The second group of particles is preferably in the form of pellets. The pellets can be of any shape, such as, for example, spheroids or ellipsoids, or may be irregularly shaped.

Suitable pellets for the initial dose and/or the second dose can be formed by, for example, depositing a layer of drug, and optional excipients, carriers, and other optional materials, onto small, pharmaceutically acceptable particles such as nonpareils. Such a layer can be deposited by methods known to those skilled in the art, such as, for example, spraying, using methods and equipment known to those skilled in the art. For example, a Wurster air suspension coater can be used. Spraying can also be accomplished using a pan coating system, wherein the drug is deposited by successive spraying accompanied by tumbling in a rotating pan. Alternatively, pellets can be formed, for either or both of the initial and delayed dose, by extrusion of the drug with suitable plasticizers and other processing aids as necessary.

Tablets or caplets, or other solid dose forms, comprising the initial dose and/or delayed dose or doses, can conveniently be administered. A solid dose form can be prepared by methods known to those skilled in the art. For example, the d-MPD, filler and other optional components may be compressed into tablets or inserted into capsules. If desired, the drug and other components of the dose form can be granulated, using processing aids, fillers, aqueous or non-aqueous solvents, and binders known to those skilled in the art. Granules can be filled into capsules, if desired. Alternatively, the d-MPD can be blended with a solvent and processed by known methods such as ball-milling, calendering, stirring, or roll-milling, then pressed into a desired shape. Suitable solvents useful in forming the particles comprising d-MPD, and other components of the dosage forms of the invention, include inert organic and inorganic solvents which do not adversely affect the components of the dosage forms. While water can be used for many drugs, including methylphenidate, useful solvents can be selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatic heterocyclic solvents, and mixtures thereof. Other solvents include acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, diglyme, and aqueous and non-aqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, and ethylene dichloride and methanol.

Following the formation of suitable particles, those particles to be used to deliver the delayed dose are then coated with a polymer-containing coating as described herein. The amount of coating to be used in forming the dosage forms, particularly the delayed dose, of the present invention, will be determined by the desired delivery properties, including the amount of drug to be delivered, the delay time required, and the size of the particles. Preferably, the coating on the particles providing the delayed dose, including all solid components of the coating such as copolymer, filler, plasticizer and optional additives and processing aids, is from about 10 percent to about 60 percent, more preferably from about 20 percent to about 50 percent, most preferably from about 30 percent to about 40 percent, of the total final weight of the particles. The appropriate amount of coating can advantageously be determined using in vitro measurements of drug release rates obtained with selected amounts of coating. The coating can be deposited by any method known to those skilled in the art, such as spray application. Spraying can be carried out by pan coating or by use of a fluid bed, such as the Wurster fluid bed described for use in depositing a drug.

After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating, to minimize or prevent interaction between the drug and the coating. Suitable sealants can be prepared from materials such as biologically inert, permeable, pharmaceutically acceptable polymers, such as, for example, hydroxypropylalkylcelluloses, wherein "alkyl" refers to C_1–C_6 hydrocarbon chains. Exemplary materials include hydroxypropyl methylcellulose, hydroxypropylethylcellulose, hydroxypropyl propylcellulose, and hydroxypropylbutylcellulose. Hydroxypropylmethylcellulose is preferred. While other materials are known to those skilled in the art for use as sealants, such as, for example, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, semipermeable cross-linked polymers such as poly (vinylbenzyltrimethyl)ammonium chloride, these are not preferred as they may affect the release rate of certain drugs including d-MPD. A sealant can be prepared by adding the material to water, and agitating for a time and at a rate sufficient to form a solution. The formation of a solution will be indicated, for example, by transparency and the absence of visually observable suspended material. The amount of material added to the water is not critical but is determined by viscosity. A solution which is too viscous will present difficulties in spraying. Generally, the amount of material should not exceed about 20 weight/volume percent, i.e., 20 g sealant material per 100 ml of water. Preferably, the

amount of material in the water is from about 5 percent to about 15 weight/ volume percent, and more preferably about 10 weight/volume percent.

Following deposition of the optional sealant and the coating, the coated particles are cured. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Stability in release rate is indicated when further curing does not affect the release rate. In contrast, instability of release rate means that as the cure time is increased, the release rate continues to vary. Curing for a sufficient time ensures that substantially the same release rate is obtained with all particles of a particular size coated with a given amount of a given coating composition. A suitable curing time can be determined by one of skill in the art without undue experimentation, by noting the variability in in vitro release times as curing time is varied. As a general guideline, many formulations can be cured in about 24 hours.

Curing can be accomplished, for example, in a forced air oven. Curing can be carried out at any temperature above room temperature, "room temperature" being defined as from about 18° C. to about 25° C. Preferably, curing is carried out at a temperature of from about 30° C. to about 50° C., more preferably from about 35° C. to about 45° C., and most preferably about 40° C. Curing time can range from several hours to several days. Preferably, the coated particles are cured for at least about 24 hours, more preferably at least about 2 days, even more preferably at least about 3 days, still more preferably at least about 4 days, still even more preferably at least about 5 days, even more preferably at least about 6 days, and most preferably for about 7 days. While no significant adverse effects or advantages have been observed when the particles are cured for longer than about 7 days, it has been found that curing for less than about 24 hours may result in relatively poorer storage stability as compared to particles cured for longer periods of time.

The amount of methylphenidate drug contained in the first and second groups of particles depends upon the prescribed dosage to be delivered to a patient. The first group of particles can consist substantially entirely of a methylphenidate drug. "Substantially entirely" means that about 95 percent or more of the weight of the first group of particles can consist of a methylphenidate drug. If desired, the first group of particles can also contain pharmaceutically acceptable carriers, excipients, and other components which do not interfere with the substantially immediate release of the medication. "Substantially immediate" release, as used herein, means that at least about 90 percent of the medication is released within about 30 minutes from the time the drug is ingested. The second group of particles can contain from about 2 percent to about 75 percent, preferably from about 4 percent to about 50 percent, medication, based on the total weight of the particles including the coating to be deposited thereon.

According to the invention, a first and a second group of particles can be administered simultaneously as part of one dosage form. Any dosage form can be used. For example, the two groups of particles can be combined within a capsule. Alternatively, the two groups of particles can be pressed into a solid form such as a tablet. In pressing the particles into a solid form, suitable processing aids known to those skilled in the art can be used. Alternatively, particles coated to provide a delayed dose of a medication can be dispersed within or blended with, the medication in powder form.

As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug. The particles comprise, in admixture with one or more binders, from about 2% to about 75% by weight of a methylphenidate drug for delayed release, and a coating comprising the pharmaceutically acceptable, substantially neutral copolymers described herein. The particles further comprise, exterior to the coating, an outer layer comprising methylphenidate drug, to provide an initial, substantially immediate, dose. The substantially immediate dose is preferably released within about 30 minutes, more preferably about 15 minutes, and most preferably within about 5 minutes following ingestion. The outer layer can optionally comprise additives such as, for example, binders, excipients, and lubricants known to those skilled in the art.

The dosage forms provided by the invention can be of any shape suitable for oral administration of a drug, such as spheroidal, cube-shaped, oval, bean shaped, or ellipsoidal. The dosage form may be in the form of granules, which may be irregularly shaped. In any of the embodiments of the present invention, although the size of the particles is generally not critical, a certain particle size or sizes can be preferred depending upon the characteristics of the dosage form. For example, the dosage form can comprise a capsule containing a first and/or second group of particles. The particles should then be of a size which allows for ease in handling, and which allows for the particles comprising a desired quantity of drug to be readily measured and inserted into the capsule. If the dosage form comprises a single group of particles providing a substantially immediate dose and a delayed dose, the particles are preferably of a size and shape which facilitate oral administration. For example, the particles can he in the form of tablets, caplets, etc. Alternatively, the particles can be contained within a capsule of suitable size and shape for oral administration. If desired, various fillers and/or binders known to those skilled in the art can be included in the particles to provide the desired size and shape.

It will be recognized by one skilled in the art that the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers, extenders, fillers, processing aids, and excipients known to those skilled in the art.

The following examples are merely illustrative of the present invention and should not be considered limiting of the scope of the invention in any way. These examples and equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure and the accompanying claims.

EXAMPLE 1

Preparation of layered pellets containing d-MPD hydrochloride

A solution of d-MPD hydrochloride was prepared as follows. To 300 grams (g) of deionized water were added 100 g of d-MPD hydrochloride, followed by moderate mixing, using a stirring paddle, for 5 minutes. A 10 percent (weight) solution of hydroxypropyl methylcellulose (HPMC E-6 from Dow Chemicals, Midland, Mich.; 250 g) was added, followed by homogenization for 5 minutes using an emulsifier head (Silverson, Chesham, UK; Model L4R). After addition of another 150 g of deionized water, the solution was sonicated for 15 minutes (Sonicor Model SC-150T; Instruments Corporation, Copiague, N.Y.), at which time the solution was clear.

A second solution was prepared by combining 300 g of deionized water and 300 g of a 10% (wt) HPMC E-6 solution and mixing for 5 minutes.

The first solution was sprayed onto 25/30 mesh non-pareil seeds (Ozone Co., Elmwood Park, N.J.) in a fluid bed apparatus (GPCG-1, Glatt Air Techniques, Inc., Ramsey, N.J.) using a Wurster head. The second solution was then sprayed to form a sealant. For both solutions, the spray rate was 8–9 g/minute. Inlet temperature was 50°–55° C. and the non-pareil seeds were maintained at 35°–40° C. Air volume was 6–7 meters per second (m/s).

EXAMPLE 2

Preparation of Coated Pellets containing d-MPD hydrochloride

A dispersion of 844 g of Eudragit® RS30D (ammoniomethacrylate copolymer from Hüls America, Somerset, N.J.; EA/MMA/TAMCl 1:2:0.1), was screened through a 60 mesh screen, then stirred for 15 minutes. A dispersion of 44 g of Eudragit® RL30D (EA/MMA/TAMCl 1:2:0.2) was similarly screened and stirred. The two dispersions were combined and stirred for 15 minutes, forming a combined dispersion. Triethyl citrate (TEC; from Moreflex, Greensboro, N.C.; 54 g) was added, followed by an additional 15 minutes of stirring. Deionized water (664 g) was added, followed by 15 minutes of stirring. Talc (108 g; from Luzenac, Englewood, Colo.) was added, followed by further stirring for 15 minutes.

The resulting combined dispersion was sprayed onto layered pellets prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 9–10 g/minute, inlet temperature 40°–45° C., and air volume 5–6 m/s. The non-pareils were maintained at 30°–35° C. during spraying. A total of 960 g of dispersion was sprayed onto the pellets, representing a 30% weight increase due to the applied coating.

EXAMPLE 3

Evaluation of drug release profile for coated pellets prepared according to Example 2

Pellets were prepared according to Example 2, varying the ratios of the polymers between 90:10 and 93:7.

Dissolution measurements

Dissolution was carried out in order to determine rate of release of d-MPD from the pellets. USP Apparatus I (United States Pharmacoepia Convention, Rockville, Md.) was used. The dissolution medium was 900 ml of deionized water (unless otherwise specified) and the temperature was maintained at 37° C. The sample cell size was 1 cm (a flow through cell), and the samples were stirred continuously at 100 rpm. The apparatus was equipped with a diode array spectrophotometer, and absorption at 220 nanometers (nanometers (run)) was measured to determine the concentration of d-MPD. Samples were measured at 60, 120, 180, 240, 360, 480, 600, 720, 840, 900, 960, 1080, 1200, 1320 and 1440 minutes.

Results of the dissolution measurements are presented in Table 1. The results indicate that the amount of drug released is influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time.

EXAMPLE 4

Comparative Example

A dispersion of 911.25 g of Eudragit® RS30D was passed through a 60 mesh screen and mixed with a similarly screened dispersion of 101.25 g of Eudragit® RL30D for 15 minutes at moderate speed. Triethyl citrate (61 g) was added, followed by an additional 15 minutes of mixing. After mixing, 991.5 g of deionized water, then 61 g of talc were added with 15 additional minutes of mixing following each addition. The resulting dispersion (1600 g) was sprayed onto 800 g of layered sealed pellets prepared according to Example 1.

No delay was observed; substantially all of the drug was released within approximately one hour. Result is shown in Table 1 (Trial 1).

EXAMPLE 5

Comparative Example

A dispersion of 600 g of Eudragit® NE30D was screened through a 60 mesh screen and mixed with a 600 g dispersion of magnesium stearate for 15 minutes at moderate speed. The resulting dispersion (750 g) was sprayed onto 750 g of layered and sealed pellets prepared according to Example 1.

After a delay of 2 hours, release of the drug was observed. About 85% of the drug was released after 14 total hours.

TABLE 1

RELEASE TIMES

Trial No.	% coat	Ratio	Delay	Talc, %	Cure time	Time for 85% release
1	40	90:10	none	20.0	24 hrs	1.0
2	30	95:5	4.0	20.0	"	8.0
3	30	95:5	4.0	20.0	"	8.0
4	30	93:7	1.0	20.0	"	3.0
5	40	93:7	1.0	20.0	"	4.0
6	30	93.5:6.5	2.0	20.0	"	5.0
7	40	"	2.0	20.0	"	5.0
8	30	94.5:5.5	2.0	20.0	"	8.0
9	40	"	1.0	20.0	"	5.0
10	30	94:6	2.0	20.0	"	5.0
11	40	"	2.0	20.0	"	5.0
12	30	95:5	2.0	40.0	"	5.0
13	40	"	3.0	40.0	"	8.0
14	30	96:4	4.0	40.0	"	10.0
15	40	"	5.0	40.0	"	10.0
16	30	"	4.0	40.0	7 days	10.0
17	20	95:5	2.0	40.0	"	5.0
18	30	"	3.0	40.0	"	6.0
19	30	"	3.0	40.0	"	6.0
20	30	"	2.0	40.0	"	6.0
21	40	"	3.0	40.0	"	8.0

What is claimed is:

1. A dosage form for the oral administration of a methylphenidate drug, comprising two groups of particles, each containing said drug, wherein:

a) said first group of particles provides a substantially immediate dose of said drug upon ingestion by a mammal, and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of said drug in admixture with one or more binders, said coating comprising a pharmaceutically acceptable ammonio methacrylate in a quantity sufficient to provide a dose of said medication delayed by from about 2 hours to about 7 hours following said ingestion.

2. The dosage form of claim **1** wherein said first group of particles comprises a pharmaceutically acceptable salt of methylphenidate in powder form.

3. The dosage form of claim 1 wherein said second group of particles comprises coated particles comprising a pharmaceutically acceptable salt of methylphenidate.

4. The dosage form of claim 2 wherein the amount of said pharmaceutically acceptable salt of methylphenidate in said first group of particles is from about 2% to about 99% by weight, based on the weight of said particles.

5. The dosage form of claim 4 wherein said pharmaceutically acceptable salt of methylphenidate comprises dl-threo methylphenidate hydrochloride.

6. The dosage form of claim 3 wherein said pharmaceutically acceptable salt of methylphenidate comprises dl-threo methylphenidate hydrochloride.

7. The dosage form of claim 1 wherein said second group of particles comprises from about 20% by weight to about 50% by weight of filler, based on the total weight of the copolymer.

8. The dosage form of claim 7 wherein said filler is selected from the group consisting of talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate.

9. The dosage form of claim 8 wherein said filler is talc.

10. The dosage form of claim 9 wherein the amount of talc is from about 35% to about 45% by weight, based on the total weight of the copolymer.

11. The dosage form of claim 10 wherein the amount of talc is from about 38% to about 42% by weight, based on the total weight of the copolymer.

12. The dosage form of claim 11 wherein the amount of talc is about 40% by weight, based on the total weight of the copolymer.

13. The dosage form of claim 1 wherein the ammonio methacrylate copolymer comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 50:1.

14. The dosage form of claim 13 wherein said ratio is from about 15:1 to about 45:1.

15. The dosage form of claim 14 wherein said ratio is from about 15:1 to about 20:1.

16. The dosage form of claim 15 wherein said ratio is from about 30:1 to about 40:1.

17. The dosage form of claim 1 comprising a first ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 30:1 to about 40:1, and a second ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 15:1 to about 20:1.

18. The dosage form of claim 17 wherein the ratio of said first copolymer to said second copolymer is from about 90:10 to about 99:1.

19. The dosage form of claim 18 wherein the ratio of said first copolymer to said second copolymer is from about 93:7 to about 97:3.

20. The dosage form of claim 19 wherein the ratio of said first copolymer to said second copolymer is about 95:5.

21. The dosage form of claim 1 wherein said delay is from about 3 hours to about 6 hours.

22. The dosage form of claim 1 wherein said delay is from about 4 hours to about 5 hours.

23. A dosage form for once-daily oral administration of a methylphenidate drug comprising:

a) particles comprising from about 2% by weight to about 99% by weight of said methylphenidate drug, in admixture with one or more binders,

b) a coating exterior to said methylphenidate drug, comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of said methylphenidate delayed by from about 2 hours to about 7 hours following administration, and

c) on the exterior surface of said coating, a layer comprising said methylphenidate drug, to provide a substantially immediate dose of said methylphenidate upon administration.

24. The dosage form of claim 23 wherein said methylphenidate is dl-threo-methylphenidate hydrochloride.

25. The dosage form of claim 23 wherein said methylphenidate is d-threo-methylphenidate hydrochloride.

26. The dosage form of claim 23 wherein said coating comprises a first ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 30:1 to about 40:1, and a second ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 15:1 to about 20:1.

27. A dosage form for the oral administration of d-threo-methylphenidate hydrochloride comprising two groups of particles, each containing d-threo-methylphenidate, wherein:

a) said first group of particles comprises d-threo-methylphenidate hydrochloride and provides a substantially immediate dose of said d-threo methylphenidate upon ingestion by a mammal, and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of d-threo-methylphenidate hydrochloride in admixture with one or more binders, said coating comprising a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a dose of said d-threo-methylphenidate delayed by from about 2 hours to about 7 hours following said ingestion.

28. A dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate providing an in vitro release profile comprising two pulses of drug release, wherein said pulses are temporally separated by from about 2 hours to about 7 hours.

29. A dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate providing an in vivo plasma concentration of said d-threo-methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about 2 hours to about 7 hours, and wherein the magnitude of said maxima differ by no more than about 30 percent.

30. A dosage form according to claim 23 wherein said ammonio methacrylate copolymer comprises a first copolymer of methyl methacrylate, ethyl acrylate and TAMCl in a ratio of 2:1:0.1 and a second copolymer of methyl methacrylate, ethyl acrylate, and TAMCl in a ratio of 2:1:0.2.

* * * * *

06-06-00



BAC

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#3

In re Application of:

JOHN G. DEVANE ET AL.

Serial No. **09/566,636**

Filed: **May 8, 2000**

For: **MULTIPARTICULATE MODIFIED RELEASE COMPOSTION**

Attorney Docket: 05990-0180

RECEIVED
JUN 0 8 2000
OFFICE OF PETITIONS
DEPUTY A/C PATENTS

PETITION FOR ACCELERATED EXAMINATION

Assistant Commissioner for Patents
Washington, DC 20231
Sir:

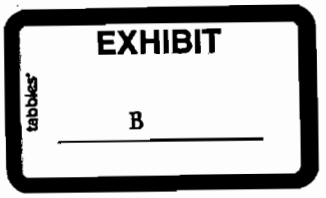
The applicant in the patent application identified above here petitions the PTO for accelerated examination of this application. This petition is filed pursuant to MPEP 708.02 (VIII) and is accompanied by the petition fee required by 37 C.F.R. § 1.17(i).

The applicant submits that the present request for accelerated examination is timely. The application has not received an action on the merits. The application is limited to a single invention for examination purposes.

The applicant with this petition submits an assignment of their invention to Elan Corporation, plc to complete their U.S. Application No. 09/566,636 filed May, 5, 2000.

The applicant with this petition submits a copy of the Search Report issued by the International Searching Authority/United States of the Patent Cooperation Treaty in a parallel application and a copy of each reference located in the Search Report. The Search Report satisfies the requirement for a pre-examination search.

A petition for accelerated examination under MPEP 708.02 (VIII) requires a detailed discussion of the search references. Fulfilling that requirement, the applicant herewith provides a summary of the invention followed by a discussion of each of the references cited in the International Searching Authority/United States of the Patent Cooperation Treaty.



EXPRESS MAIL LABEL NO. EL561435407US

Summary the Invention

The following discussion pertains to the claims as originally filed.

The present invention as claimed defines a multiparticulate modified release composition having at least two populations of particles containing active ingredient. At least one of the populations of particles has a modified release coating or a modified release material matrix present in the composition to permit delivery of the active ingredient following oral administration in a pulsatile manner. The ability to provide a dosage form capable of producing a pulsed or bimodal release *in vivo* is particularly advantageous for school children who require dosing during the middle of the school day. The dosage form of the present invention is particularly advantageous for methylphenidate and other controlled substances which require secured storage on the premises of schools or other institutions.

Prior Art

U.S. Patent No. 5,445,829 (Paradissis, *et al.*) was cited as a category X reference relevant to claims 1-4, 6, 10, 11, 12, 21, 22, 27, 33, and 34 and a category Y reference relevant to claims 12, and 14-18. Paradassis, et al. is not relevant to the present invention because there is no disclosure or suggestion of a pulsed release profile. While Paradassis, *et al.* does combine extended release particles with immediate release particles, the release profile obtained is described as extended release over a twelve to twenty-four hour time period. In contrast, the capability of producing a pulsed release profile *in vivo* is a major objective of the present invention.

U.S. Patent No. 5,837,284 (Mehta, *et al.*) is cited as categories A and P relevant to claims 1-36. Applicants would like to point out that the Mehta, *et al.* references discloses a formulation that is capable of a delayed release profile *in vitro*, but there is not disclosure of a formulation that produces an *in vivo* pulsed release profile.

U.S. Patent No. 4,888,178 (Rotini, *et al.*) is cited as a category Y reference relevant to claims 1-36. This reference relates solely to a mixed granulation of naproxen and is not relevant to the present invention. The mixed granulation produces a release of active ingredient *in vivo*

that is therapeutically effective over twenty-four hours and is therefore suitable for once a day administration.

U.S. Patent No. 4,904,476 (Mehta, *et al.*) is cited as a category Y references relevant to claims 1-36. This references discloses a formulation comprising a three component system which produces three distinct release profiles.

U.S. Patent No. 5,158,777 (Abramowitz, *et al.*) is cited as a category Y reference relevant to claims 1-36. This reference relates to a captopril formulation which combines a pH stabilized core coated with an enteric component which is them combined with an IR component. The completed formulation does not produce a pulsatile release profile. It is known that captopril is poorly absorbed in the colon. Thus, the formulation described in this reference is designed particularly to provide a pH stable core of captopril for delayed release in the colon.

No amendment to the claims has been made.

The applicant submits that the foregoing fully complies with the requirements of MPEP 708.02 (VIII), and requests that the PTO grant this petition and accelerate the examination of this application. The Commissioner is hereby authorized to charge any additional fees required under 37 CFR §1.17(i), or credit any overpayment to Account No. 10-1215.

Respectfully submitted,

Leona G. Young

By: Leona G. Young
Reg. No. 37,266

JONES & ASKEW, LLP
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3424 Peachtree Road NE
Atlanta, Georgia 30326
(404) 949-2400
Attorney Docket: 05990-0180

PATENT COOPERATION TREATY

RECEIVED
FEB 15
PCT 99.1816, PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To: MARLA J. CHURCH
1300 GOULD DRIVE
GAINESVILLE, GEORGIA 30504

OIPE
JUN 05 2000
PATENT & TRADEMARK OFFICE JC93

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing *(day/month/year)* 18 FEB 2000
Applicant's or agent's file reference 99.1816.US	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US99/25632	International filing date *(day/month/year)* 01 NOVEMBER 1999
Applicant CHURCH, MARLA J.	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JAMES M. SPEAR
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/220 (January 1994)*

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 99.1816.US	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/25632	International filing date *(day/month/year)* 01 NOVEMBER 1999	(Earliest) Priority Date *(day/month/year)* 02 NOVEMBER 1998
Applicant CHURCH, MARLA J.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [ ] **The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing**
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. **The figure of the drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25632

A. * CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 9/20, 9/24, 9/54, 9/58, 9/62
US CL :424/458, 461, 462, 464, 468, 472, 494, 497
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/458, 461, 462, 464, 468, 472, 494, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,445,829 A (PARADISSIS et al) 29 August 1995, see column 3, lines, 20-62, column 5, column 6, lines 33-45, column 7, line 4 through column 8, line 35, column 9, lines 16-44, examples 1-5.	1 - 4 , 6 , 1 0 , 11,12,21,22, 27,33,34 --- 12,14-18
A,P	US 5,837,284 A (MEHTA et al) 17 November 1998, see column 3, column 7, lines 12-32, column 9, lines 23-68, column 12, lines 15-35, examples 1 and 2.	1-36
Y	US 4,888,178 A (ROTINI et al) 19 December 1989, see entire document.	1-36
Y	US 4,904,476 A (MEHTA et al) 27 February 1990, see entire document.	1-36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
02 FEBRUARY 2000

Date of mailing of the international search report
18 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
JAMES M. SPEAR
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25632

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,158,777 A (ABRAMOWITZ et al) 27 October 1992, see entire document.	1-36

Technology Center to which it may subsequently be transferred; exemplary situations include new cases transferred as the result of a telephone election and cases transferred as the result of a timely reply to any official action.

(F) Applications which appear to interfere with other applications previously considered and found to be allowable, or which will be placed in interference with an unexpired patent or patents.

(G) Applications ready for allowance, or ready for allowance except as to formal matters.

(H) Applications which are in condition for final rejection.

(I) Applications pending more than 5 years, including those which, by relation to a prior United States application, have an effective pendency of more than 5 years. See MPEP § 707.02.

(J) Reexamination proceedings, MPEP § 2261 >and § 2661<.

See also MPEP § 714.13, § 1207 and § 1309.

708.02 Petition To Make Special [R-6]

37 CFR 1.102. Advancement of examination.

(a) Applications will not be advanced out of turn for examination or for further action except as provided by this part, or upon order of the Director to expedite the business of the Office, or upon filing of a request under paragraph (b) of this section or upon filing a petition under paragraphs (c) or (d) of this section with a showing which, in the opinion of the Director, will justify so advancing it.

(b) Applications wherein the inventions are deemed of peculiar importance to some branch of the public service and the head of some department of the Government requests immediate action for that reason, may be advanced for examination.

(c) A petition to make an application special may be filed without a fee if the basis for the petition is:

(1) The applicant's age or health; or

(2) That the invention will materially:

(i) Enhance the quality of the environment;

(ii) Contribute to the development or conservation of energy resources; or

(iii) Contribute to countering terrorism.

(d) A petition to make an application special on grounds other than those referred to in paragraph (c) of this section must be accompanied by the fee set forth in § 1.17(h).

New applications ordinarily are taken up for examination in the order of their effective United States filing dates. Certain exceptions are made by way of petitions to make special, which may be granted under the conditions set forth below. Any statement in support of a petition to make special must be based on a good faith belief that the invention in fact qualifies for special status. See 37 CFR 1.56 and 10.18.

Any petition to make special, other than those based on applicant's health or age or the Patent Prosecution Highway (PPH) pilot program, filed on or after August 25, 2006 must meet the requirements for the revised accelerated examination program set forth in MPEP § 708.02(a). See subsections III and IV below for the requirements for filing a petition to make special based on applicant's health or age.

Applications filed prior to August 25, 2006 are not eligible for the revised accelerated examination program set forth in MPEP § 708.02(a). Until August 25, 2006, applicant may file a petition to make special in an application filed prior to August 25, 2006 by complying with the guidelines and requirements set forth in subsections I-II, and V-XII below.

A petition to make special filed on or after August 25, 2006 will only be granted if it is based upon applicant's health or age or is under the PPH pilot program, or if it complies with the requirements set forth in MPEP § 708.02(a).

I. MANUFACTURE

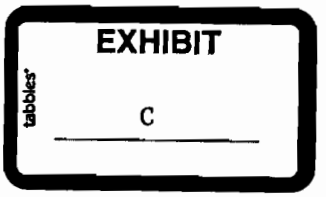
An application may be made special on the ground of prospective manufacture upon the filing of a petition accompanied by the fee under 37 CFR 1.17(h) and a statement by the applicant, assignee or an attorney/agent registered to practice before the Office alleging:

(A) The possession by the prospective manufacturer of sufficient presently available capital (stating approximately the amount) and facilities (stating briefly the nature thereof) to manufacture the invention in quantity or that sufficient capital and facilities will be made available if a patent is granted;

If the prospective manufacturer is an individual, there must be a corroborating statement from some responsible party, as for example, an officer of a bank, showing that said individual has the required available capital to manufacture;

(B) That the prospective manufacturer will not manufacture, or will not increase present manufacture, unless certain that the patent will be granted;

(C) That the prospective manufacturer obligates himself, herself or itself, to manufacture the invention, in the United States or its possessions, in quantity immediately upon the allowance of claims or



issuance of a patent which will protect the investment of capital and facilities; and

(D) That the applicant or assignee has made or caused to be made a careful and thorough search of the prior art, or has a good knowledge of the pertinent prior art.

Applicant must provide one copy of each of the references deemed most closely related to the subject matter encompassed by the claims if said references are not already of record.

II. INFRINGEMENT

Subject to a requirement for a further showing as may be necessitated by the facts of a particular case, an application may be made special because of actual infringement (but not for prospective infringement) upon payment of the fee under 37 CFR 1.17(h) and the filing of a petition accompanied by a statement by the applicant, assignee, or an attorney/agent registered to practice before the Office alleging:

(A) That there is an infringing device or product actually on the market or method in use;

(B) That a rigid comparison of the alleged infringing device, product, or method with the claims of the application has been made, and that, in his or her opinion, some of the claims are unquestionably infringed; and

(C) That he or she has made or caused to be made a careful and thorough search of the prior art or has a good knowledge of the pertinent prior art.

Applicant must provide one copy of each of the references deemed most closely related to the subject matter encompassed by the claims if said references are not already of record.

Models or specimens of the infringing product or that of the application should not be submitted unless requested.

III. APPLICANT'S HEALTH

An application may be made special upon a petition by applicant accompanied by any evidence showing that the state of health of the applicant is such that he or she might not be available to assist in the prosecution of the application if it were to run its normal course, such as a doctor's certificate or other medical certificate. No fee is required for such a petition. See 37 CFR 1.102(c).

Personal/medical information submitted as evidence to support the petition will be available to the public if the application file and contents are available to the public pursuant to 37 CFR 1.11 or 1.14. If applicant does not wish to have this information become part of the application file record, the information must be submitted pursuant to MPEP § 724.02.

IV. APPLICANT'S AGE

An application may be made special upon filing a petition including any evidence showing that the applicant is 65 years of age, or more, such as ** applicant's statement >or a statement from a registered practitioner that he or she has evidence that the applicant is 65 years of age or older<. No fee is required with such a petition. See 37 CFR 1.102(c).

Personal/medical information submitted as evidence to support the petition will be available to the public if the application file and contents are available to the public pursuant to 37 CFR 1.11 or 1.14. If applicant does not wish to have this information become part of the application file record, the information must be submitted pursuant to MPEP § 724.02.

V. ENVIRONMENTAL QUALITY

The U.S. Patent and Trademark Office will accord "special" status to all patent applications for inventions which materially enhance the quality of the environment of mankind by contributing to the restoration or maintenance of the basic life-sustaining natural elements, i.e., air, water, and soil.

All applicants desiring to participate in this program should petition that their applications be accorded "special" status. The petition under 37 CFR 1.102 must state that special status is sought because the invention materially enhances the quality of the environment of mankind by contributing to the restoration or maintenance of the basic life-sustaining natural elements. No fee is required for such a petition. See 37 CFR 1.102(c). If the application disclosure is not clear on its face that the claimed invention materially enhances the quality of the environment by contributing to the restoration or maintenance of one of the basic life-sustaining natural elements, the petition

must be accompanied by a statement under 37 CFR 1.102 by the applicant, assignee, or an attorney/agent registered to practice before the Office explaining how the materiality standard is met. The materiality standard does not permit an applicant to speculate as to how a hypothetical end-user might specially apply the invention in a manner that could materially enhance the quality of the environment. Nor does such standard permit an applicant to enjoy the benefit of advanced examination merely because some minor aspect of the claimed invention may enhance the quality of the environment.

VI. ENERGY

The U.S. Patent and Trademark Office will, on petition, accord "special" status to all patent applications for inventions which materially contribute to (A) the discovery or development of energy resources, or (B) the more efficient utilization and conservation of energy resources. Examples of inventions in category (A) would be developments in fossil fuels (natural gas, coal, and petroleum), hydrogen fuel technologies, nuclear energy, solar energy, etc. Category (B) would include inventions relating to the reduction of energy consumption in combustion systems, industrial equipment, household appliances, etc.

All applicants desiring to participate in this program should petition that their applications be accorded "special" status. The petition under 37 CFR 1.102 must state that special status is sought because the invention materially contributes to category (A) or (B) set forth above. No fee is required for such a petition, 37 CFR 1.102(c). If the application disclosure is not clear on its face that the claimed invention materially contributes to category (A) or (B), the petition must be accompanied by a statement under 37 CFR 1.102 by the applicant, assignee, or an attorney/agent registered to practice before the Office explaining how the materiality standard is met. The materiality standard does not permit an applicant to speculate as to how a hypothetical end-user might specially apply the invention in a manner that could materially contribute to category (A) or (B). Nor does such standard permit an applicant to enjoy the benefit of advanced examination merely because some minor aspect of the claimed invention may be directed to category (A) or (B).

VII. INVENTIONS RELATING TO RECOMBINANT DNA

In recent years revolutionary genetic research has been conducted involving recombinant deoxyribonucleic acid ("recombinant DNA"). Recombinant DNA research appears to have extraordinary potential benefit for mankind. It has been suggested, for example, that research in this field might lead to ways of controlling or treating cancer and hereditary defects. The technology also has possible applications in agriculture and industry. It has been likened in importance to the discovery of nuclear fission and fusion. At the same time, concern has been expressed over the safety of this type of research. The National Institutes of Health (NIH) has released guidelines for the conduct of research concerning recombinant DNA. These "Guidelines for Research Involving Recombination DNA Molecules," were published in the *Federal Register* of July 7, 1976, 41 FR 27902-27943. NIH is sponsoring experimental work to identify possible hazards and safety practices and procedures.

In view of the exceptional importance of recombinant DNA and the desirability of prompt disclosure of developments in the field, the U.S. Patent and Trademark Office will accord "special" status to patent applications relating to safety of research in the field of recombinant DNA. Upon appropriate petition and payment of the fee under 37 CFR 1.17(h), the Office will make special patent applications for inventions relating to safety of research in the field of recombinant DNA. Petitions for special status should be accompanied by statements under 37 CFR 1.102 by the applicant, assignee, or statements by an attorney/agent registered to practice before the Office explaining the relationship of the invention to safety of research in the field of recombinant DNA research. The fee set forth under 37 CFR 1.17(h) must also be paid.

VIII. SPECIAL EXAMINING PROCEDURE FOR CERTAIN NEW APPLICATIONS — ACCELERATED EXAMINATION

A new application (one which has not received any examination by the examiner) may be granted special status provided that applicant (and this term includes applicant's attorney or agent) complies with each of the following items:

(A) Submits a petition to make special accompanied by the fee set forth in 37 CFR 1.17(h);

(B) Presents all claims directed to a single invention, or if the Office determines that all the claims presented are not obviously directed to a single invention, will make an election without traverse as a prerequisite to the grant of special status.

The election may be made by applicant at the time of filing the petition for special status. Should applicant fail to include an election with the original papers or petition and the Office determines that a requirement should be made, the established telephone restriction practice will be followed.

If otherwise proper, examination on the merits will proceed on claims drawn to the elected invention.

If applicant refuses to make an election without traverse, the application will not be further examined at that time. The petition will be denied on the ground that the claims are not directed to a single invention, and the application will await action in its regular turn.

Divisional applications directed to the nonelected inventions will not automatically be given special status based on papers filed with the petition in the parent application. Each such application must meet on its own all requirements for the new special status;

(C) Submits a statement(s) that a pre-examination search was made, listing the field of search by class and subclass, publication, Chemical Abstracts, foreign patents, etc. The pre-examination search must be directed to the invention as claimed in the application for which special status is requested. A search made by a foreign patent office satisfies this requirement if the claims in the corresponding foreign application are of the same or similar scope to the claims in the U.S. application for which special status is requested;

(D) Submits one copy each of the references deemed most closely related to the subject matter encompassed by the claims if said references are not already of record; and

(E) Submits a detailed discussion of the references, which discussion points out, with the particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is patentable over the references.

In those instances where the request for this special status does not meet all the prerequisites set forth above, applicant will be notified and the defects in the request will be stated. The application will remain in the status of a new application awaiting action in its regular turn. In those instances where a request is defective in one or more respects, applicant will be given *one* opportunity to perfect the request in a renewed petition to make special. If perfected, the request will then be granted. If not perfected in the first renewed petition, any additional renewed petitions to make special may or may not be considered at the discretion of the Technology Center (TC) Special Program Examiner.

Once a request has been granted, prosecution will proceed according to the procedure set forth below; there is no provision for "withdrawal" from this special status.

The special examining procedure of VIII (accelerated examination) involves the following procedures:

(A) The new application, having been granted special status as a result of compliance with the requirements set out above will be taken up by the examiner before all other categories of applications except those clearly in condition for allowance and those with set time limits, such as examiner's answers, etc., and will be given a complete first action which will include *all* essential matters of merit as to all claims. The examiner's search will be restricted to the *subject matter encompassed by the claims*. A first action rejection will set a 3-month shortened period for reply.

(B) During the 3-month period for reply, applicant is encouraged to arrange for an interview with the examiner in order to resolve, with finality, as many issues as possible. In order to afford the examiner time for reflective consideration before the interview, applicant or his or her representative should cause to be placed in the hands of the examiner at least one working day prior to the interview, a copy (clearly denoted as such) of the amendment that he or she proposes to file in response to the examiner's action. Such a paper will not become a part of the file, but will form a basis for discussion at the interview.

(C) Subsequent to the interview, or responsive to the examiner's first action if no interview was had, applicant will file the "record" reply. The reply at this stage, to be proper, must be restricted to the rejections, objections, and requirements made. Any amendment which would require broadening the search field will be treated as an improper reply.

(D) The examiner will, within 1 month from the date of receipt of applicant's formal reply, take up the application for final disposition. This disposition will constitute either a final action which terminates with the setting of a 3-month period for reply, or a notice of allowance. The examiner's reply to any amendment submitted after final rejection should be prompt and by way of form PTOL-303, by passing the application to issue, or by an examiner's answer should applicant choose to file an appeal brief at this time. The use of these forms is not intended to open the door to further prosecution. Of course, where relatively minor issues or deficiencies might be easily resolved, the examiner may use the telephone to inform the applicant of such.

(E) A personal interview after a final Office action will not be permitted unless requested by the examiner. However, telephonic interviews will be permitted where appropriate for the purpose of correcting any minor outstanding matters.

After allowance, these applications are given top priority for printing. See MPEP § 1309.

IX. SPECIAL STATUS FOR PATENT APPLICATIONS RELATING TO SUPERCONDUCTIVITY

In accordance with the President's mandate directing the U.S. Patent and Trademark Office to accelerate the processing of patent applications and adjudication of disputes involving superconductivity technologies when requested by the applicant to do so, the U.S. Patent and Trademark Office will, on request, accord "special" status to all patent applications for inventions involving superconductivity materials. Examples of such inventions would include those directed to superconductive materials themselves as well as to their manufacture and application. In order that the U.S. Patent and Trademark Office may implement this procedure, we invite all applicants desiring to participate in this program to request that their applications be accorded "special" status. Such requests should be accompanied by a statement under 37 CFR 1.102 that the invention involves superconductive materials. No fee is required.

X. INVENTIONS RELATING TO HIV/AIDS AND CANCER

In view of the importance of developing treatments and cures for HIV/AIDS and cancer and the desirability of prompt disclosure of advances made in these fields, the U.S. Patent and Trademark Office will accord "special" status to patent applications relating to HIV/AIDS and cancer.

Applicants who desire that an application relating to HIV/AIDS or cancer be made special should file a petition and the fee under 37 CFR 1.17(h) requesting the U.S. Patent and Trademark Office to make the application special. The petition for special status should be accompanied by a statement explaining how the invention contributes to the diagnosis, treatment or prevention of HIV/AIDS or cancer.

XI. INVENTIONS FOR COUNTERING TERRORISM

In view of the importance of developing technologies for countering terrorism and the desirability of prompt disclosure of advances made in these fields, the U.S. Patent and Trademark Office will accord "special" status to patent applications for inventions which materially contribute to countering terrorism.

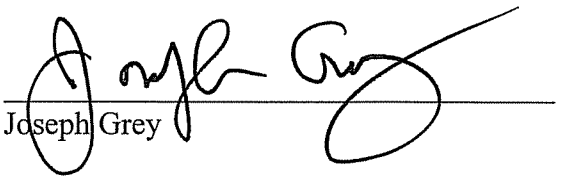
International terrorism as defined in 18 U.S.C. 2331 includes "activities that - (A) involve violent acts or acts dangerous to human life that are a violation of the criminal laws of the United States or of any State, or that would be a criminal violation if committed within the jurisdiction of the United States or of any State; [and] (B) appear to be intended - (i) to intimidate or coerce a civilian population; (ii) to influence the policy of a government by intimidation or coercion; or (iii) to affect the conduct of a government by assassination or kidnapping..." The types of technology for countering terrorism could include, but are not limited to, systems for detecting/identifying explosives, aircraft sensors/security systems, and vehicular barricades/disabling systems.

All applicants desiring to participate in this program should petition that their applications be accorded special status. The petition under 37 CFR 1.102 must state that special status is sought because the invention materially contributes to countering terrorism. No fee is required for such a petition. See 37 CFR 1.102(c). If the application disclosure is not clear on its face that the claimed invention is materially

CERTIFICATE OF SERVICE

I, Joseph Grey hereby certify that, on this 17th day of December, 2007, and in addition to the service provided by the Court's CM/ECF system, true and correct copies of the foregoing Response to Motion to Dismiss were served by first class United States mail, postage prepaid, upon counsel at the following address:

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