Trials@uspto.gov
571-272-7822

Paper 29
Entered: July 31, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ALKERMES PHARMA IRELAND LIMITED,
Patent Owner.

Case IPR2018-00943
Patent 7,919,499 B2

Before CHRISTOPHER M. KAISER, JACQUELINE T. HARLOW, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge.*

DECISION
Granting Joint Motion to Terminate
35 U.S.C. § 317(a) and 37 C.F.R. § 42.74

APOTEX EXHIBIT 1002 (Part 1 of 2)
Apotex v. Alkermes
IPR2025-00514

On July 30, 2019, pursuant to the Board's authorization, Amneal Pharmaceuticals LLC ("Petitioner") and Alkermes Pharma Ireland Limited ("Patent Owner") filed a joint motion to terminate this *inter partes* review pursuant to 35 U.S.C. § 317(a) and 37 C.F.R. § 42.74. Paper 27 ("Motion" or "Mot."). The motion was accompanied by a true, unredacted copy of a Settlement and License Agreement (Ex. 2058), and a joint request to treat the Settlement and License Agreement as business confidential information, to be kept separate from the patent file, pursuant to 35 U.S.C. § 317(b) and 37 C.F.R. § 42.74(c) (Paper 28).

The parties represent in their joint motion that they "have settled their disputes" and have "executed a Settlement and License Agreement that authorizes the Parties to seek termination of this *inter partes* review." Mot. 2. Additionally, the parties state that the patent-at-issue in this proceeding, U.S. Patent No. 7,919,499 B2 ("the '499 patent"), is not involved in any related district court litigations, or in any related *inter partes* review proceedings. *Id.*

The Board generally expects that a case "will terminate after the filing of a settlement agreement, unless the Board has already decided the merits." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,768 (Aug. 14, 2012); *see also* 37 C.F.R. § 42.72. Here, although the Board has instituted an *inter partes* review of claims 1–13 of the '499 patent, the Board has not heard oral argument and has not decided the merits of the proceeding.

Under the circumstances presented here, therefore, we determine that it is appropriate to terminate this proceeding with respect to both Petitioner and Patent Owner. Accordingly, we grant the parties' joint motion to terminate.

We also determine that the parties have complied with the requirements of 37 C.F.R. § 42.74(c) to have the Settlement and License Agreement treated as business confidential information and kept separate from the files of the patent-at-issue in this proceeding. Thus, we grant the joint request to treat the Settlement and License Agreement as business confidential.

Accordingly, it is

ORDERED that the joint motion to terminate the proceeding is GRANTED;

FURTHER ORDERED that the joint request to treat the parties' Settlement and License Agreement as business confidential information, to be kept separate from the patent file, is GRANTED; and

FURTHER ORDERED that the instant proceeding is TERMINATED.

FOR PETITIONER:

Tedd W. Van Buskirk
Michael H. Teschner
Kendall K. Gurule
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
litigation@lernerdavid.com
tvanbuskirk@lernerdavid.com
mteschner.ipr@ldlkm.com
kgurule@lernerdavid.com

FOR PATENT OWNER:

Naveen Modi
Bruce M. Wexler
Michael Stramiello
Joseph M. O'Malley Jr.
Gerard A. Salvatore
PAUL HASTINGS LLP
PH-Amneal-Alkermes-IPR@paulhastings .com
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
michaelstramiello@paulhastings.com
josephomalley@paulhastings.com
gerardsalvatore@paulhastings.com

Trials@uspto.gov
571-272-7822

Paper No. 8
Entered: November 7, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ALKERMES PHARMA IRELAND LIMITED,
Patent Owner.

Case IPR2018-00943
Patent 7,919,499 B2

Before CHRISTOPHER M. KAISER, JACQUELINE T. HARLOW, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Amneal Pharmaceuticals LLC ("Petitioner") requests an *inter partes* review of claims 1–13 of U.S. Patent No. 7,919,499 B2 ("the '499 patent," Ex. 1001). Paper 1 ("Pet."). Alkermes Pharma Ireland Limited ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1355–56 (2018). Moreover, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial) ("USPTO Guidance").

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '499 patent is unpatentable. Accordingly, we institute an *inter partes* review of all challenged claims (1–13) of the '499 patent, based on all grounds raised in the Petition.

II. BACKGROUND

A. Related Matters

The parties state that there are no pending judicial proceedings involving the '499 patent. Pet. 61; Paper 6, 1. Patent Owner states that U.S. Patent Application No. 15/486,869 claims priority to the '499 patent and is currently pending before the Office. Paper 6, 1.

B. The '499 Patent

The '499 patent, titled "Naltrexone Long Acting Formulations and Methods of Use," issued on April 5, 2011. Ex. 1001, at [45]. The '499 patent relates to "a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long-acting formulation comprising naltrexone." *Id.*, at [57].

According to the '499 patent, "[a]lcohol dependence is a chronic disorder that results from a variety of genetic, psychological and environmental factors." *Id.* at 1:13–14. The '499 patent states that, "[i]n the past, most rehabilitative treatments have been psychosocial." *Id.* at 1:18–19. But, "[w]ith advances in neurobiology, there is increasing interest in drug therapy for alcohol dependence," such as naltrexone therapy. *Id.* at 1:19–27.

The '499 patent states that "[t]he inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone." *Id.* at 1:31–33. Specifically, "[t]his invention arose from the unexpected discovery that substantially improved serum levels of naltrexone can be achieved by administering long acting formulations of naltrexone, such as the Alkermes, Inc. formulation, Vivitrex® injectable suspension, made employing its Medisorb® delivery system." *Id.* at 2:29–34.

In one embodiment, the "invention includes a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone." *Id.* at 2:22–25. The formulation dosage preferably ranges from about 310 to about 480 mg of naltrexone. *Id.* at 1:45–46. The '499 patent states that the long acting formulation "may be achieved through the use of polymers (preferably poly-lactide or poly-lactide-co-glycolide polymers) to entrap or encapsulate the naltrexone." *Id.* at 3:11–16. The '499 patent identifies a preferred polylactide-co-glycolide ("PLGA") polymer as MEDISORB® 7525 DL polymer. *Id.* at 5:43–46; 6:44–51.

The '499 patent states that the disclosed method unexpectedly achieves a serum AUC of naltrexone that is "preferably at least about three times" that achieved by 50 mg/day oral administration of naltrexone. *Id.* at 2:22–28. The '499 patent provides a "semi-quantitative comparison" of the efficacy of long-acting naltrexone with oral naltrexone. *See id.* at 18:4–19:34 (Example 3). The '499 patent states that "oral naltrexone significantly decreased the relapse rate by 36% relative to placebo," whereas "Vivitrex suspension 380 mg significantly decreased the relapse rate by 45% relative to placebo." *Id.* at 18:57–67.

C. Illustrative Claim

Petitioner challenges the patentability of claims 1–13, but not claims 14 and 15, of the '499 patent. Of the challenged claims, claim 1 is independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is about three times

greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

Ex. 1001, 21:2–9.

D. The Prior Art

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the '499 patent:

1. Sandra D. Comer et al., *Depot naltrexone: long-lasting antagonism of the effects of heroin in humans*, 159(4) PSYCHOPHARMACOLOGY 351–30 (2002) ("Comer," Ex. 1010);

2. Elie S. Nuwayser, U.S. Patent No. 7,157,102 B1 (issued Jan. 2, 2007) ("Nuwayser," Ex. 1014);

3. G. Rubio et al., *Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment*, 36(5) ALCOHOL & ALCOHOLISM 419–25 (2001) ("Rubio," Ex. 1028);

4. Steven G. Wright et al., U.S. Patent No. 6,264,987 B1 (issued July 24, 2001) ("Wright," Ex. 1018);

5. Henry R. Kranzler et al., *Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study*, 22(5) ALCOHOLISM CLINICAL & EXPERIMENTAL RES. 1074–79 (1998) ("Kranzler," Ex. 1011);

6. Alkermes, Inc., *Form 10-K: Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934* (July 2002) ("Alkermes 10-K," Ex. 1016); and

7. U.S. Trademark Application No. 76/271,990 for Vivitrex (Aug. 2002) ("Vivitrex Specimen," Ex. 1017).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–13 of the '499 patent on the following grounds:

Claims	Basis	Reference(s)
1, 3–5, and 10–12	35 U.S.C. § 102	Comer
1, 3–5, 11, and 12	35 U.S.C. § 102	Nuwayser
1–13	35 U.S.C. § 103	Comer, Nuwayser, Rubio, and Wright
1–13	35 U.S.C. § 103	Nuwayser, Comer, Rubio, and Wright
1–13	35 U.S.C. § 103	Nuwayser, Kranzler, Rubio, and Wright
1–13	35 U.S.C. § 103	Alkermes 10-K, Vivitrex Specimen, Wright, and Rubio

Pet. 4. Petitioner also relies on the Declaration of Kinam Park, Ph.D. *See id.* (citing Exs. 1030; 1031). Patent Owner disputes that Petitioner's asserted grounds render the challenged claims unpatentable. *See generally* Prelim. Resp.

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we address claim construction. Third, we provide an overview of the asserted references. Fourth, taking account of the information presented, we consider whether the grounds asserted in the Petition meet the threshold showing for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends, and Dr. Park testifies, that a person of ordinary skill in the art would have a

doctorate level degree in pharmaceutics or related formulation sciences (such as a Pharm.D. or Ph.D.) and at least two years of experience in controlled release formulation. Pet. 15–16; Ex. 1030 ¶¶ 28–31. Petitioner and Dr. Park also contend that "[a] lesser degree of formal education balanced by additional practical experience could also qualify as a [person of ordinary skill in the art]." *Id.* In response, Patent Owner states that it "does not necessarily disagree with [Petitioner's] proposed definition of a [person of skill in the art] and reserves the right to offer another definition should the Board institute trial." Prelim. Resp. 15 n.8 (citations omitted).

We adopt Petitioner's definition for purposes of this decision. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art). Further, based on the information presented at this stage of the proceeding, we consider Petitioner's declarant—Dr. Park—qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1031 (Dr. Park's curriculum vitae).

B. Claim Interpretation

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Petitioner proposes interpretations for claim terms: "a long acting formulation," "the serum AUC of naltrexone . . . than that achieved by 50 mg/day oral administration," "about three," "five or more days," "initial oral dose," and "about 35% by weight." Pet. 16–21. In response, Patent Owner asserts that Petitioner's claim interpretations are unnecessary or incorrect. Prelim. Resp. 62–63.

To determine whether to institute an *inter partes* review, we need not explicitly interpret every claim term for which Petitioner proposes a construction. *See* 35 U.S.C. § 314(a); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."). We determine that, to resolve whether Petitioner has demonstrated a reasonable likelihood of prevailing, we need only address Petitioner's proposed interpretations of "the serum AUC of naltrexone . . . than that achieved by 50 mg/day oral administration" and "about three."

1. *"the serum AUC of naltrexone . . . than that achieved by 50 mg/day oral administration"*

Claim 1 recites that "the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration." Ex. 1001, 21:6–7. Petitioner asserts that the '499 patent does not define "AUC," but, relying on the declaration testimony of Dr. Park, asserts that an ordinarily skilled artisan would understand serum "AUC" to refer to "area under the curve." Pet. 17 (citing Ex. 1030 ¶¶ 36, 37, 56–59). Petitioner also asserts that an ordinarily skilled artisan would understand that serum AUC "is merely the area under the curve created by plotting plasma drug concentration versus time." *Id.* (citing Ex. 1030 ¶¶ 38, 60).

We agree with Petitioner's interpretation of serum "AUC." As the record reflects, AUC is a well-known pharmacokinetic parameter referring to area under the curve. We also agree with Petitioner that serum AUC is represented by a plasma concentration-time curve. *See, e.g.*, Ex. 1012, 3 (referring to "AUC" as "area under plasma concentration-time curve"); Ex. 1044, 261–62 (accord); *see also* Ex. 1044, 261 (stating that AUC is used to evaluate the extent of drug absorption).

By its plain terms, claim 1 requires that the serum AUC achieved by parenterally administering the long-acting formulation of naltrexone (i.e., a long-acting formulation comprising about 310 mg to about 480 mg naltrexone and a polylactide-co-glycolide polymer as a biocompatible polymer) is about three times the serum AUC achieved by administration of a 50 mg/day oral naltrexone formulation. Ex. 1001, 21:3–9. Petitioner asserts that the '499 patent "does not define or specify the AUC of the claimed formulation or oral dosing." Pet. 17. Because of this lack of information, Petitioner asserts, "a POSA must look to the art" but "would find . . . that there is no single accepted data set, particularly for the AUC resulting from administering 50 mg/day orally." Pet. 17–18. Petitioner asserts therefore that "the BRI . . . allows the use of *any data* for the AUC of the claimed naltrexone dose compared to *any data* for the AUC of a 50 mg/day oral dose." *Id.* at 18–19 (citing Ex. 1030 ¶ 43) (emphases added).

We agree with Petitioner that the '499 patent does not provide a value (or underlying data) for the serum AUC of the disclosed long-acting formulation of naltrexone, or a value (or underlying data) for the serum AUC of the 50 mg/day oral formulation. *See* Pet. 17–18. We observe, instead, that the written description describes the serum AUC of the

disclosed long-acting formulation of naltrexone in comparative terms: as "preferably at least about three times . . . greater over the course of the month than that achieved by 50 mg/day oral administration" of naltrexone. Ex. 1001, 1:37–40.[1]

Even so, we disagree with Petitioner on this record that the broadest reasonable interpretation allows for the use of *any* available data set for the claimed serum AUCs. Pet. 18–19. Petitioner does not address the '499 patent's prosecution history in its claim construction analysis. But in interpreting claims, "[a] patent's specification, together with its prosecution history, constitutes intrinsic evidence to which the Board *gives priority* when it construes claims." *WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1323 (Fed. Cir. 2018) (emphasis added). Thus, we must "consult the patent's prosecution history in proceedings" such as this one, "in which the patent has been brought back to the agency for a second review." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017) (*en banc*).

During prosecution of the '499 patent, applicants filed a Declaration under 37 C.F.R. § 1.132 ("the Ehrich Declaration") purporting to show unexpected results for the serum AUC of the claimed long-acting naltrexone formulation over that of a 50 mg/day oral formulation (i.e., an unexpected

[1] The written description of the '499 patent also refers to the claimed serum AUC of the long-acting naltrexone formulation as "unexpected," Ex. 1001, 2:29, and further states that "the pharmacokinetic profile of long-acting injectable naltrexone differs substantially from that of the oral formulation," *id.* at 17:49–51.

serum AUC differential). Ex. 1003, 1–18. The Ehrich Declaration provides two data sets (Cohort A and Cohort B) for the serum AUCs of the claimed long-acting naltrexone formulation and the 50 mg/day oral naltrexone. *See id.* at 6 (Table 8). For Cohort A, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.307,[2] which is 3.37 times the serum AUC value of 1.278 for the 50 mg oral naltrexone dose. *Id.* at 2. Similarly, for Cohort B, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.921, which is 3.35 times the 1.468 serum AUC value for the 50 mg oral naltrexone dose. *Id.* In her Statement of Reasons for Allowance, the Examiner referenced this data as showing "an AUC about three times greater than that achieved by 50 mg/day oral administration," and explained that "no prior art disclos[es]" this effect. Ex. 1009, 4.

Because these serum AUC data points were presented during prosecution and were relied on by the Examiner in allowing the application issuing as the '499 patent, an ordinarily skilled artisan would understand that the serum AUC achieved by 50 mg/day oral administration encompasses these data points. Indeed, Dr. Park admits that "[b]ecause the patent provides no data, a POSA would look at the Ehrich Declaration." Ex. 1030 ¶ 72. For purposes of this decision, therefore, we interpret the reference to a "50 mg/day" AUC in "than that achieved by 50 mg/day oral administration"

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[2] The Declaration explains that the $AUC_{0\text{-}t}$ ($AUC_{0\text{-}28days}$) for a single dose of 380 mg long-acting naltrexone formulation on a per day basis can be calculated for Cohort A by dividing 120.6 ng•day/ml (the $AUC_{0\text{-}t}$ for Cohort A) by 28 days (120.6÷28=4.307), and by dividing 137.8 ng•day/ml (the $AUC_{0\text{-}t}$ for Cohort B) by 28 days (137.8÷28=4.921). Ex. 1003, 2.

as encompassing at least serum AUCs of 1.278 ng•day/ml and 1.468 ng•day/ml.

We acknowledge Petitioner's arguments and evidence suggesting that the comparative AUC values for the claimed long-acting naltrexone formulation and the 50 mg/day oral naltrexone render the claims difficult to understand. For example, Petitioner asserts that "the art reports varying data sets for oral dosing, none of which is consistent." Pet. 18 (citing Ex. 1030 ¶¶ 41, 81–86). Dr. Park cites to Baek[3] for showing a serum AUC of 1.80 ng•day/ml and 1.810 ng•day/ml for the 50 mg/day oral naltrexone formulations having the trade names Levia and Traxone, respectively. Ex. 1030 ¶ 82 (citing Ex. 1039, 72 (Table 1)). And Dr. Park points out that the serum AUC of the 380 mg long-acting naltrexone formulation would not be about three times the serum AUC of either Levia or Traxone. *See id.* ¶ 83 (calculating the serum AUC of the claimed 380 mg long-acting naltrexone formulation as 2.4 times the serum AUC of the Traxone 50 mg/day oral formulation).

Although Petitioner's arguments may raise issues of claim clarity—or even indefiniteness—that are beyond the scope of this *inter partes* review, because we discern, based on the present record, that the serum AUC of a 50 mg/day oral formulation encompasses at least the values reported in the Ehrich Declaration, we determine, for purposes of this decision, that the phrase is broad enough to create a reasonable likelihood that it reads on the prior art that is asserted here. *See infra* §§ III.D., III.E. Thus, it is

[3] In-hwan Baek et al., Evaluation of the Bioequivalence of Two Brands of Naltrexone 50 mg Tablet in Healthy Volunteers, 16(1) KOR. J. CLIN. PHARM. 69–74 (2006) ("Baek," Ex. 1039).

unnecessary at this point to determine the precise contours of the claim limitation for purposes of this decision. *Vivid Techs.*, 200 F.3d at 803. We leave for trial the issue of whether, on a fully developed record, this term is capable of construction, as well as the final construction it should be given. Accordingly, the parties are encouraged to explore this issue further at trial.

2. *"about three"*

Turning to the claim language "about three," we agree with Petitioner that—although not defined in the '499 patent—"about three necessarily encompasses at least 3.3" and "at least about 2.7." Pet. 19 (citing Ex. 1030 ¶¶ 45–47) (quotations omitted). As Petitioner points out, the Ehrich Declaration provides data of a serum AUC for long-acting naltrexone formulation that is 3.3 times greater than that achieved by oral dosing. *Id.*; Ex. 1003, 2. Dr. Park also testifies, and supports with evidence, that the term "about" as used in the art "indicate[s] a quantity within 10%." Ex. 1030 ¶ 47 (citing Ex. 1043, 8). For these reasons, we agree with Petitioner that the broadest reasonable interpretation of "about three" encompasses values as high as 3.3 and as low as 2.7.

C. Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. *Comer*

Comer describes a study "designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®)" in subjects dependent on heroin. Ex. 1010, 351 (Abstract). Comer states that the results of the study "suggest that th[e] depot formulation of naltrexone

provides a safe, effective, long-lasting antagonism of the effects of heroin." *Id.*

As background, Comer states that, although approved as a treatment for heroin dependence, "naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment." *Id.* at 351 (Abstract). Comer states, however, that "[s]ustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness." *Id.* at 352. In particular, "[a] new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side effects." *Id.* Comer states that "[a]lthough this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin." *Id.* Thus, "[t]he purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the effects of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone." *Id.*

Comer states that naltrexone microcapsules were reconstituted in a suspending medium and 2.4 ml of the suspension was injected into study participants. *Id.* at 354. Participants given a "low dose" received one placebo injection and one naltrexone injection (192 mg naltrexone base) subcutaneously into the buttocks using an 18 gauge needle. *Id.* Participants given a "high dose" received two naltrexone injections (384 naltrexone base). *Id.* Figure 1 of Comer, reproduced below, provides mean plasma levels of naltrexone as a function of depot naltrexone dosage and dates after administration of depot naltrexone. *Id.*

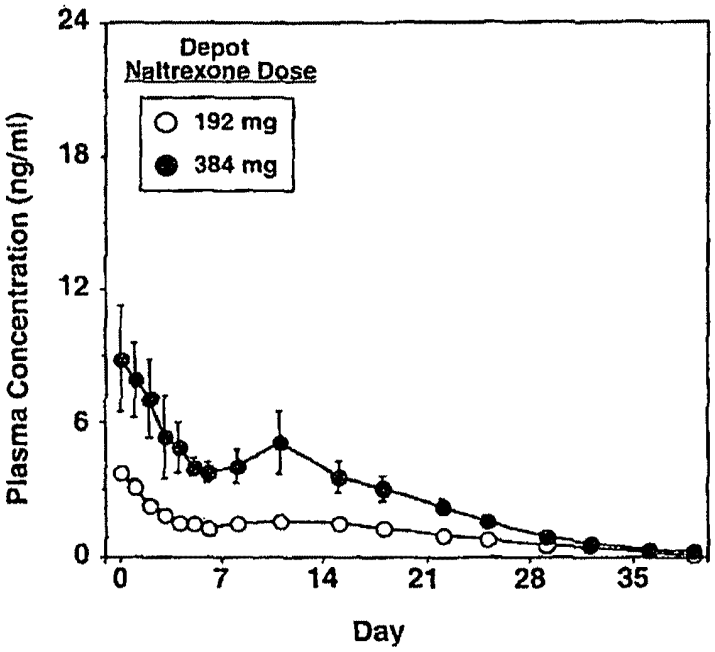


Figure 1 shows mean plasma levels of depot naltrexone over time following either a 192 mg depot dose (○) or a 384 mg depot dose (●). Ex. 1010, 354.

Comer states that "[a]cross the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were 3.8 (±0.2) and 8.9 (±1.4) ng/ml, respectively." *Id.* at 358. Comer states that a comparative study "reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone)." *Id.* Thus, Comer states, "the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day)." Even so, "antagonism of heroin's effects occurred, despite negligible plasma levels of naltrexone." *Id.*

Comer summarizes that "the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects." *Id.* at 359. And thus, "a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications." *Id.*

2. *Nuwayser*

Nuwayser teaches a multi-layered microcapsule containing one or more active ingredients and a process for preparing the microcapsule. Ex. 1014, Abstract. In Example IV, Nuwayser teaches the preparation of naltrexone microcapsules by coating naltrexone microspheres with the polymer poly-L-(–)-lactide-co-glycolide (PLGA). *Id.* at 19:3–25. Nuwayser teaches that the microcapsules contain a final naltrexone content of 54.4%. *Id.* "This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days." *Id.* Figure 7 of Nuwayser, reproduced below, provides mean plasma levels of naltrexone "after single and double [subcutaneous] injections of Depotrex™." *Id.*

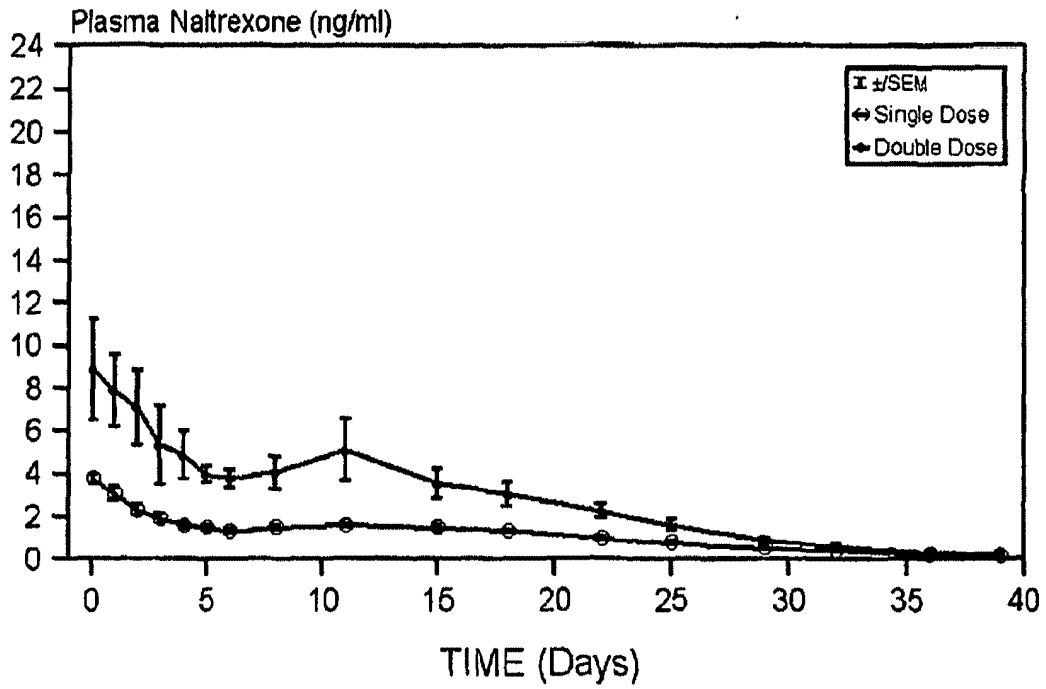


Figure 7 shows mean plasma levels of naltrexone over time following either a single dose (○) or a double dose (●) of naltrexone. Ex. 1014.

3. *Rubio*

Rubio states that both naltrexone and acamprosate "reduce relapse in alcohol dependence," but they "have not yet been compared in a published trial." Ex. 1028, 419 (Abstract). Rubio describes a study designed "to compare the efficacy of these compounds in conditions similar to those in routine clinical practice." *Id.* Recently detoxified alcohol-dependent men were administered either one year of treatment with 50 mg/day of naltrexone (i.e., one tablet per day) or 1665–1998 mg/day of acamprosate (i.e., six tablets per day). *Id.*; *see also id.* at 420. Rubio found that, at the end of the year, "[n]altrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate." *Id.* at 422.

4. *Wright*

Wright teaches a method for preparing microparticles having a selected polymer molecular weight. Ex. 1018, Abstract. In Example 3, Wright teaches the preparation of microparticles containing naltrexone. *Id.* at 7:50–8:60. Wright teaches that the polymers used were "MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6535 DL polymer." *Id.* at 7:56–58.

5. *Kranzler*

Kranzler describes a "preliminary study" of the use of sustained-release naltrexone for alcoholism treatment. Ex. 1011, 1074 (Abstract). In Kranzler's study, twenty alcohol-dependent subjects received 50 mg/day oral naltrexone for two weeks, followed by a medication-free two-week "washout period." *Id.* at 1074–75. Fifteen of those subjects then received a single subcutaneous injection of 206 mg of a sustained-release preparation (SRP) of naltrexone, and five received placebo. *Id.* The SRP of naltrexone comprises biodegradable, injectable microcapsules. *Id.* at 1074. Kranzler states that "[a]fter injection, [naltrexone] concentrations exceeded a mean of 1 ng/ml for 21 days," and that "[a]dverse effects produced by the SRP of [naltrexone] were comparable with those resulting from oral [naltrexone] therapy." *Id.* at 1074, Abstract. Kranzler concludes that "[t]he results of this preliminary study support the potential clinical utility of the SRP of [naltrexone] for treatment of alcohol dependence." *Id.*

6. *Alkermes 10-K*

Alkermes 10-K states that "we are developing Vivitrex™, a Medisorb formulation of naltrexone, for the treatment of alcoholism and opiate dependence." Ex. 1016, 3. Alkermes 10-K states that naltrexone is "an

FDA-approved drug used for the treatment of alcohol and opioid dependence, which is currently available in daily oral dosage form." *Id.* at 5. Alkermes 10-K states that "Vivitrex is based on our Medisorb injectable extended-release technology and is designed to provide once-a-month dosing to enhance patient adherence by removing the need for daily dosing." *Id.*

7. *Vivitrex Specimen*

The "Vivitrex Specimen" consists of an "Allegation of Use of a Mark under 15 U.S.C. §§ 1051(c) or (d)," filed in U.S. Trademark Application No. 76/271,990 for "Vivitrex," accompanied by one specimen of the mark as used in commerce, a transmittal letter, and a fee. Ex. 1017, 1–5. The Allegation states that the mark was "first used at least as early as August 7, 2002; and was first used in commerce at least as early as August 7, 2002." *Id.* at 4. The specimen of the mark appears to be a label for Vivitrex, which identifies the contents as "Medisorb® Naltrexone (190 mg or 380 mg) (for injectable suspension)." *Id.* at 5.

D. Asserted Anticipation Grounds

Petitioner contends that Comer, as evidenced by Nuwayser, anticipates claims 1, 3–5, and 10–12 of the '499 patent. Pet. 22–26. Petitioner also contends that Nuwayser anticipates claims 1, 3–5, 11, and 12. *Id.* at 26–27. A claim is anticipated, and therefore unpatentable under 35 U.S.C. § 102, if all of its limitations are disclosed either explicitly or inherently in a single prior art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all the limitations of the claim "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). We address each asserted anticipation ground individually below.

1. *Anticipation by Comer as Evidenced by Nuwayser*

Petitioner argues that Comer "teaches the method of claim 1—treating patients in need of naltrexone (heroin dependent patients) by parenterally administering (depot injection into the buttocks) a long-acting (1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) [naltrexone] and PLGA (evidenced by Nuwayser)." Pet. 23–24 (citing Ex. 1030 ¶ 89). Petitioner argues that Comer teaches the claimed serum AUC differential of about 3, by comparing Comer's serum AUC values with the Ehrich Declaration's serum AUC values for 50 mg/day oral naltrexone in Cohort A. Pet. 24 (citing Ex. 1030 ¶¶ 67–74, 81, 89). Petitioner also argues that Comer inherently teaches the claimed AUC differential because (1) Comer's dose is 384 mg, which is about the claimed dose of 380 mg, and (2) Patent Owner admitted before the Office during prosecution of a related patent application that serum AUC is dose dependent. *Id.* at 24–25 (citing Ex. 1030 ¶¶ 81, 89). Having considered the

arguments and evidence before us, we find that the record establishes a reasonable likelihood that Petitioner would prevail on its asserted ground of anticipation by Comer, as evidenced by Nuwayser.

Specifically, we are satisfied on this record that Comer teaches, either explicitly or inherently, each and every limitation of claim 1. As to the preamble ("method for treating an individual in need of naltrexone"), Comer discloses administering naltrexone to opioid-dependent patients, and discloses that naltrexone is a treatment for heroin dependence. Ex. 1010, 351 (Abstract). As to the method step ("parenterally administering a long-acting formulation comprising about 310 mg to about 480 mg of naltrexone"), Comer discloses giving two naltrexone injections of 192 mg naltrexone base (for a total of 384 mg) into the buttocks of patients. *Id.* at 354. And, as to the composition of the long-acting formulation ("where the biocompatible polymer is a polylactide-co-glycolide polymer"), Comer discloses "[a] new depot formulation of naltrexone (Depotrex®)" "that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side effects." *Id.*

As to this latter limitation, we agree with Petitioner on this record that an ordinarily skilled artisan would understand Comer's "Depotrex®" formulation refers to "naltrexone and a biocompatible polymer . . . wherein the biocompatible polymer is a polylactide-co-glycolide polymer," as recited in claim 1. *See* Pet. 22–23. Specifically, Nuwayser describes the preparation of naltrexone microcapsules by coating naltrexone microspheres with poly-L-(-)-lactide-co-glycolide polymer. Ex. 1014, 19:3–25. Nuwayser then states that "[t]his formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (see Fig. 7)." *Id.* at

19:23–25. Turning to Figure 7, Nuwayser refers to "single and double [subcutaneous] injections of Depotrex™." *Id.*, Fig. 7. Taken together, these passages identify Depotrex as a formulation comprising naltrexone and a poly-lactide-co-glycolide polymer, and thus an ordinarily skilled artisan would understand that Comer's Depotrex also refers to a formulation comprising naltrexone and a poly-lactide-co-glycolide polymer.

Turning to the remaining limitation of claim 1 ("wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration"), we are satisfied—on this record and for institution—that Comer teaches the serum AUC differential either explicitly or inherently. On the present record, we credit and rely on Dr. Park's calculation of Comer's serum AUC as 103.7 ng•day/ml, based on his analysis of Figure 1 using Photoshop software. *See* Ex. 1030 ¶¶ 67–74. Dr. Park explains that this serum AUC is 2.9 (or "about three") times the serum AUC achieved by 50 mg/day oral naltrexone in Cohort A of the Ehrich Declaration. Ex. 1030 ¶ 72.[4] Alternatively, Dr. Park explains that, because AUC is dose dependent and Comer administers about the same dose of long-acting naltrexone, Comer inherently teaches the same or substantially the same serum AUC values. *Id.* ¶ 70 (citing Ex. 1027, 7). Dr. Park reasonably supports this analysis by showing that Comer's AUC value of 103.7 ng•day/ml is "statistically the same" as the Ehrich Declaration's 120.6 ng•day/ml AUC value, given that the Ehrich Declaration discloses a mean standard deviation of 19.6. *Id.* (citing Ex. 1003, 6).

[4] Specifically, the serum AUC of Comer's 384 mg naltrexone dose is 3.703 (103.7 ng•day/ml÷28 days), which is 2.90 times the 1.278 serum AUC value for Cohort A's 50 mg oral naltrexone dose. Ex. 1030 ¶ 72.

On this record, we are not persuaded by any of Patent Owner's arguments and evidence that Petitioner has failed to show a reasonable likelihood of prevailing on this anticipation ground. *See* Prelim. Resp. 15–30. As an initial matter, Patent Owner argues that the anticipation ground is improper because it relies on multiple references. *Id.* at 16–17, 26–30, 32–33. But it appears, at least on this record, that Petitioner relies permissibly on Nuwayser to show that an ordinarily skilled artisan would have understood Comer's "Depotrex®" to be the same "Depotrex™" disclosed in Nuwayser: a formulation comprising naltrexone and polylactide-co-glycolide polymer. *See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 727 (Fed. Cir. 1984) (explaining that, although anticipation must be found in a single reference, a "caveat to that rule permit[s] the use of additional references to interpret the allegedly anticipating reference"). Put differently, we view Nuwayser as evidencing what an ordinarily skilled artisan would have understood Comer's reference to "Depotrex" to have meant; not as supplementing missing limitations in Comer.

Patent Owner asserts that, in any event, Petitioner has failed to show that Comer's "Depotrex®" is, in fact, the same "Depotrex™" in Nuwayser. Prelim. Resp. 26–30. In particular, Patent Owner asserts that "different versions of 'depotrex' existed" as of Comer's publication date, and that Petitioner has presented no evidence about which particular formulation Comer studied. *Id.* at 28–29. Patent Owner also asserts that Comer expressly states that "the same formulation of depot naltrexone used in the present study was also tested by Kranzler," yet Kranzler describes a formulation containing a dose of 206 mg in 2.4 ml solution, whereas Comer

describes Depotrex as containing "a dose of 192 mg in 2.4 ml." *Id.* at 29 (citing Ex. 1010, 354; Ex. 1011, 1075).

Having considered the arguments and evidence before us, we are of the opinion that Patent Owner's arguments highlight disputed issues of fact about whether an ordinarily skilled artisan would have understood Comer's "Depotrex®" formulation to comprise polylactide-co-glycolide as the biocompatible polymer. We conclude that this issue is best resolved following trial with the benefit of a full record, keeping in mind that Petitioner bears the burden of proving that the claims are unpatentable for anticipation. *See* 37 C.F.R. § 42.108(c) (requiring certain "genuine issue[s] of material fact" to "be viewed in the light most favorable to the petitioner . . . for the purpose of deciding whether to institute an *inter partes* review").

Patent Owner's remaining arguments go to whether Comer teaches the claimed serum AUC differential of "about three." See Prelim. Resp. 19–26. In short, Patent Owner argues that "there is no evidence in either the literature or Dr. Park's declaration that Photoshop is an acceptable means for calculating AUC or that Dr. Park's odd use of this software produces accurate results." *Id.* at 22–23. To the extent that Patent Owner's arguments raise admissibility issues under Federal Rule of Evidence (FRE) 702(c), we note that the admissibility of evidence is usually determined at trial upon filing a motion to exclude. *See* 37 C.F.R. §§ 42.64(b)(1) ("Any objection to evidence submitted during a preliminary proceeding must be filed within ten business days of the institution of trial."), 42.64(c) ("[a] motion to exclude must be filed to preserve any objection"). And to the extent that Patent Owner's arguments relate to the weight we should give to Dr. Park's

analysis under 37 C.F.R. § 42.65(a), we determine that this issue is best resolved following trial with the benefit of a full record.

In summary, based on the record before us and the application of the reasonable likelihood standard, we are satisfied that Petitioner has shown sufficiently for instituting trial that it would prevail in showing claim 1 unpatentable for anticipation by Comer, as evidenced by Nuwayser. Patent Owner does not raise additional arguments specific to dependent claims 3–5 and 10–12 at this stage of the proceeding. *See generally* Prelim. Resp. We have reviewed Petitioner's contentions and supporting evidence regarding claims 3–5, and 10–12 as well, and find them sufficient based on the current record for claims 3–5 and 12. *See* Pet. 25 (citing Ex. 1030 ¶¶ 81, 89, 91), 26 (citing Ex. 1010, 354; Ex. 1030 ¶¶ 94).

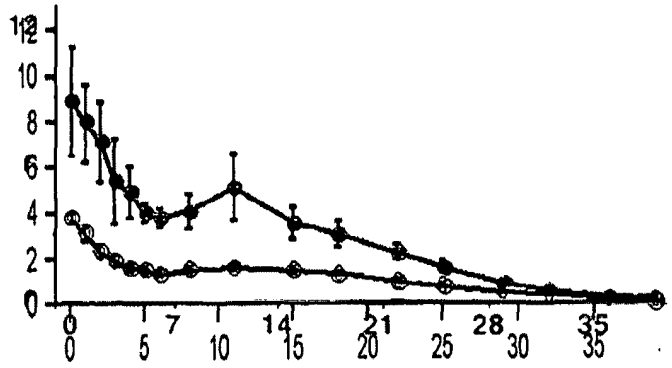
On this record, however, we question whether dependent claims 10 and 11, in particular, are properly challenged for anticipation. For example, claim 10 specifies that the patient is alcohol dependent. Ex. 1001, 22:6–7. Comer does not appear to teach (and at most appears to merely suggest) treating alcohol-dependent patients with a long-acting formulation of naltrexone. *See* Ex. 1010, 352 (stating that naltrexone had already been established to be safe and effective in alcoholics). Nevertheless, in light of *SAS*, the USPTO Guidance, and our determination that Petitioner has met its burden as to its challenge of claim 1, we also determine that it is appropriate to institute *inter partes* review of the remaining challenged claims (3–5 and 10–12) for anticipation by Comer, as evidenced by Nuwayser.

2. *Anticipation by Nuwayser*

We now turn to Petitioner's anticipation challenge based on Nuwayser, which is substantially similar to that based on Comer as

evidenced by Nuwayser. Taking claim 1 as illustrative, Petitioner argues that "Nuwayser describes a formulation of PLGA (65% LA:35% GA) and 54.4% naltrexone, described as Depotrex, which, when administered subcutaneously, delivered therapeutic levels in six heroin addicts for 30 days." Pet. 26 (citing Ex. 1014, 14:26–50, 19:4–25; Ex. 1030 ¶¶ 95–97). We agree with Petitioner on this record that Nuwayser teaches expressly treating an individual in need of naltrexone with a naltrexone formulation comprising polylactide-co-glycolide as a biocompatible polymer. Ex. 1014, 19:4–25.

Nuwayser does not teach expressly the claimed dosage range (310 to 480 mg), nor the claimed serum AUC differential (about three). *See* Ex. 1014, 19:23–25 (stating that six heroin addicts were administered a "therapeutic level of naltrexone" but not specifying the dosage). But, relying on Dr. Park's Declaration, Petitioner argues that Nuwayser teaches these limitations inherently because Figure 7 of Nuwayser and Figure 1 of Comer provide the same pharmacokinetic plots. *Id.* (citing Ex. 1030 ¶¶ 75–77, 96). Dr. Park asserts that "a POSA would recognize that the Nuwayser AUC is exactly the same as the Comer AUC" because Figures 1 and 7 are "drawn from the same data." Ex. 1030 ¶ 76. Dr. Park creates a figure superimposing Figure 7 onto Figure 1, adjusting the X and Y dimensions to match the sizes:



Id. ¶ 77. Dr. Park concludes that, because the curves are the same, Nuwayser must necessarily disclose the same dose (380 mg) and the same AUC differential (about 3) as Comer. *Id.* ¶¶ 76–77.

Having considered the arguments and evidence before us, we share Patent Owner's concern that Petitioner uses "circular logic" to support its anticipation challenge based on Nuwayser. *See* Prelim. Resp. 31 (citing Pet. 26–27). Specifically, Patent Owner points out that Petitioner's argument comes down to: "the plasma plots in Nuwayser and Comer are allegedly the same so the dose must be the same, and because the dose is the same the AUC must be the same." Prelim. Resp. 26. In light of *SAS* and USPTO Guidance, however, we institute *inter partes* review on the ground of anticipation by Nuwayser for challenged claims (1, 3–5, 11, and 12).

E. Asserted Obviousness Grounds over Comer, Nuwayser, Rubio, and Wright

Petitioner contends that claims 1–13 are unpatentable as obvious over the combination of Comer in view of Nuwayser, Rubio, and Wright, Pet. 29–36, and over the combination of Nuwayser in view of Comer, Rubio, and Wright, *id.* at 36–39. A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that

the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

1. *The Claimed Limitations*

Because these two obviousness grounds are substantially identical, we chose to address them together. Taking claim 1 as illustrative, we are satisfied on this record that Petitioner establishes sufficiently for institution that the combination of Comer and Nuwayser teach each and every limitation of the claim. Specifically, Comer discloses treating opioid-dependent patients with naltrexone by giving two naltrexone injections of 192 mg naltrexone base (for a total of 384 mg) into the buttocks of patients using a needle. Ex. 1010, 351–54. As to the composition of the long-acting formulation ("wherein the biocompatible polymer is a polylactide-co-glycolide polymer"), Comer discloses "[a] new depot formulation of naltrexone (Depotrex®) . . . that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side effects." *Id.* at 352. Nuwayser discloses a formulation comprising PLGA (65% LA:35% GA) and 54.4% naltrexone— also called Depotrex™—delivered at "therapeutic levels" to heroin addicts. Ex. 1014, 19:4–25.

We are not persuaded, on this record, by Patent Owner's argument that "neither Comer nor Nuwayser cures the deficiencies of the other."

Prelim. Resp. 34–35. For example, Patent Owner's argument that "[n]either reference discloses 'treating' someone in need of naltrexone" because "[t]reatment would . . . never involve providing an addict with several ascending doses of heroin," *id.* at 34, lacks evidentiary support. Even so, Patent Owner appears to concede that Nuwayser gives a "therapeutic level" of a naltrexone-PGLA formulation to heroin addicts. *Id.* at 34; *see also* Ex. 1014, 19:23–25. Patent Owner's remaining arguments—that Comer fails to disclose the claimed AUC profile and that Nuwayser fails to disclose the claimed dose—are not persuasive for the same reasons explained above in connection with Petitioner's anticipation grounds. *See supra* § III.D.

On this record and at this stage of the proceeding, therefore, we are satisfied that Petitioner establishes sufficiently for institution that the combination of Comer and Nuwayser satisfies the limitations of claim 1. We have reviewed Petitioner's contentions and supporting evidence regarding claims 2–13 as well, and find them sufficient based on the current record. *See* Pet. 33–36 (Comer in view of Nuwayser), 38–39 (Nuwayser in view of Comer). For example, we agree with Petitioner that Rubio teaches treating alcoholics with naltrexone for a period of 12 months, and thus teaches the limitations of claims 2 and 10. Pet. 33, 35, 38, 39; Ex. 1028, 419–20.

2. *Motivation to Combine/Reasonable Expectation of Success*

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck*

& Cie v. Gnosis S.P.A., 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

Relying on the Dr. Park's Declaration, Petitioner contends that an ordinarily skilled artisan would have had a reason to combine the teachings of Comer and Nuwayser with a reasonable expectation of success. Pet. 30–33 (Comer in view of Nuwayser), 37–38 (Nuwayser in view of Comer). As to the combination of Comer in view of Nuwayser, Petitioner contends that, even "[i]f one did not accept that Nuwayser defined Depotrex to a POSA . . . , a POSA would nonetheless be motivated to use the Nuwayser naltrexone formulation in the method taught by Comer with a reasonable expectation of success." *Id.* at 29–30 (citing Ex. 1030 ¶ 102). And, as to the combination of Nuwayser in view of Comer, Petitioner contends that "[t]he only thing that Nuwayser arguably does not disclose is dose," and therefore, an ordinarily skilled artisan "looking for an appropriate dose" would have been motivated "to use that disclosed in Comer, namely 384 mg (about 380 mg)." *Id.* at 36–37 (citing Ex. 1030 ¶ 106). Petitioner also contends that these combinations lead to successful therapeutic doses of naltrexone. *Id.* at 31, 37.

Having considered the arguments and evidence before us, we are satisfied on this record that Petitioner has shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to combine the disclosures of Comer and Nuwayser to provide an improved method for treating an individual in need of naltrexone. Specifically, we agree with Petitioner that an ordinarily skilled artisan looking to replicate Comer's

naltrexone microcapsules, Ex. 1010, 354, would have had a reason to look to Nuwayser, because Nuwayser expressly discloses a method for preparing naltrexone microcapsules that can be administered therapeutically to heroin addicts, Ex. 1014, 19:4–25. Moreover, on this record, we are persuaded that an ordinarily skilled artisan looking for dosing information to achieve Nuwayser's serum AUC results would have had a reason to use the dose disclosed in Comer, given that Comer discloses the successful administration of Depotrex to heroin-dependent patients. Pet. 37 (citing Ex. 1030 ¶ 106); Ex. 1010, 351 (stating that "[t]hese results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin").

Although we acknowledge Patent Owner's arguments that no reason exists to combine Comer and Nuwayser, we are not persuaded by those arguments on this record. *See* Prelim. Resp. 33–38. For example, Patent Owner argues that an ordinarily skilled artisan seeking to formulate Comer's injectable naltrexone dosage form would have looked, at most, to Kranzler, because "Comer expressly states that the same formulation was used in Kranzler." *Id.* at 36 (citing Ex. 1010, 359); *see also id.* at 40–42. But even if Comer suggests looking to Kranzler, that suggestion would not necessarily dissuade the skilled artisan from seeking out other forms of Depotrex found in the prior art, such as that disclosed in Nuwayser. *See In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) (teaching a way does not necessarily teach away).

We are also not persuaded by Patent Owner's argument that "[h]ow a POSA would find Nuwayser is not explained," Prelim. Resp. 35, because "[t]he person of ordinary skill is a hypothetical person who is presumed to

be aware of all the pertinent prior art." *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). And here, both Comer and Nuwayser are pertinent to each other, because both disclose long-acting naltrexone formulations and both use those formulations to treat opioid addiction. Ex. 1010, 351; Ex. 1014, 19:23–25.

Finally, we are persuaded on this record that Petitioner has shown sufficiently for instituting trial that the ordinarily skilled artisan would have had a reasonable expectation of success in the combination of Comer and Nuwayser. Specifically, we note that both Comer and Nuwayser state that their depot formulations of naltrexone delivered therapeutic levels of naltrexone to patients in need of treatment. Specifically, Comer states that "[t]hese results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin." Ex. 1010, 351. And Nuwayser states that "[t]his formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (see FIG. 7)." Ex. 1014, 19:23–25.

We are not persuaded on this record, however, by Petitioner's argument that "even if the claimed AUC differential did not result from this combination, the claims would still be obvious because this limitation should be given little weight." Pet. 31 (citing Ex. 1030 ¶¶ 16, 63–65, 81–86, 106–107); *see also id.* at 11–12, 31–33. Even if, as Dr. Park testifies, as little as 1 ng/ml of naltrexone is sufficient to deliver therapeutic levels of naltrexone over a period of 28 days, *see, e.g.*, Ex. 1030 ¶ 60), we are unaware of any principle of law that would allow us to disregard the claimed serum AUC differential as simply "inconsequential," Pet. 2.

3. *Summary*

In sum, we are satisfied that Petitioner establishes a reasonable likelihood that it would prevail in showing that claim 1 is unpatentable under 35 U.S.C. § 103 as obvious over the combination of Comer in view of Nuwayser, Rubio, and Wright, and over the combination of Nuwayser in view of Comer, Rubio, and Wright. In light of *SAS* and USPTO Guidance, we also institute *inter partes* review of dependent claims 2–13 on the same grounds.

F. Asserted Obviousness Ground over Nuwayser, Kranzler, Rubio, and Wright

Petitioner contends that the challenged claims are unpatentable as obvious over Nuwayser in view of Kranzler, Rubio, and Wright. *See* Pet. 39–43. Specifically, Petitioner contends that—even if Nuwayser fails to teach the claimed dose—"[i]t would be obvious to determine the dose that resulted in the disclosed AUC without undue experimentation by generating a standard curve." Pet. at 40 (citing Ex. 1030 ¶ 116). Alternatively, Petitioner contends that Kranzler's disclosed 206 mg dose "would provide at least a starting point for a POSA" to increase the dose until the claimed AUC differential (about three) is achieved. Pet. 40–41. Petitioner also contends that—even if Nuwayser fails to disclose the claimed AUC differential—the "claims are obvious." *Id.*

Having considered the arguments and evidence before us, we find that the record fails to establish a reasonable likelihood that Petitioner would prevail on this asserted ground. For example, Petitioner's statement that "[i]t would require nothing more than routine experimentation to prepare an AUC-dose standard curve to find a dose for any given AUC," Pet. 40, lacks specific and credible evidentiary support. So too Petitioner's assertion that

"the dose should be adjustable as needed and should render the claimed AUC differential obvious." Pet. 41. Such conclusory statements fail to satisfy Petitioner's burden in showing obviousness. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

Moreover, Dr. Park's Declaration does not adequately support Petitioner's argument that the ordinarily skilled artisan would create a standard AUC curve to determine a particular dose. Pet. 40–41. For example, Dr. Park states summarily that "a POSA knows how to confirm that they have arrived at the correct dose" and a "POSA can easily conduct an experiment to establish a standard curve . . . correlating the AUC as a function of dose." Ex. 1030 ¶ 116. But Dr. Park does not support these statements with any details about how these calculations would be performed, or provide any specific evidence supporting these statements. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

Nevertheless, we institute *inter partes* review of all challenged claims (1–13) for obviousness over Nuwayser in view of Kranzler, Rubio, and Wright in light of *SAS* and the USPTO Guidance.

G. Asserted Obviousness Ground over Alkermes 10-K, Vivitrex Specimen, Rubio, and Wright

Turning to the final asserted ground of unpatentability, Petitioner asserts that claims 1–13 are unpatentable as obvious over Alkermes 10-K, in view of Vivitrex Specimen, Rubio, and Wright. *See* Pet. 44–50. Petitioner asserts that an ordinarily skilled artisan, reading Alkermes 10-K, would have observed the disclosure of "Vivitrex™" in connection with an injectable extended-release formulation of naltrexone, and would have been motivated

to investigate whether Alkermes had filed for trademark registration of "Vivitrex" based on the "™" signal. *Id.* at 45. That investigation, Petitioner asserts, would have led the ordinarily skilled artisan to USPTO records, where she would "find an application and Vivitrex Specimen," which discloses "Medisorb® Naltrexone (190 mg or 380 mg) for injectable suspension." *Id.* at 46 (citing Ex. 1017, 5; Ex. 1030 ¶ 130). Petitioner then asserts that the artisan would have turned to Wright, which "explains the Medisorb technology and how it can be used to produce, *inter alia*, naltrexone microparticles from PLGA." *Id.* at 46 (citing Ex. 1018, 7:48–8:60; Ex. 1030 ¶ 131). Finally, Petitioner asserts that, "[b]ased on Wright, a POSA could make three different types of PLGA naltrexone microparticles," and that "at least one of these three particles . . . would result in the same AUC as identified in the '499 patent." *Id.* at 47 (citing Ex. 1018, 1:33–38; Ex. 1030 ¶¶ 132–134). Having considered the arguments and evidence before us, however, we again find that the record fails to establish a reasonable likelihood that Petitioner would prevail on this asserted ground.

1. *Printed Publication*

As an initial matter, we agree with Patent Owner that Petitioner's asserted ground fails because Petitioner did not meet its burden to show that at least Alkermes 10-K qualifies as a printed publication. Prelim. Resp. 48–51. Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may only challenge the claims of a patent based on "prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Petitioner has the initial burden of production to establish that there is prior art that renders the challenged claims unpatentable. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015) (citing *Tech. Licensing*

Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008)). For institution purposes, Petitioner has the burden to establish a reasonable likelihood that it will prevail on the merits, which includes, *inter alia*, making a sufficient showing in the Petition that the relied-upon references qualify as "printed publications" within the meaning of 35 U.S.C. §§ 102 and 311(b). *Cf.* 35 U.S.C. § 314(a).

Whether a reference qualifies as a "printed publication" involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The Federal Circuit has explained that public accessibility is the "touchstone in determining whether a reference constitutes a 'printed publication.'" *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). A reference is considered "publicly accessible" upon a satisfactory showing that the reference has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it." *In re Wyer*, 655 F.2d 221, 226 (CCPA 1981).

To establish that Alkermes 10-K is prior art to the '499 patent, Petitioner asserts that Alkermes 10-K was electronically filed on the Securities and Exchange Commission's EDGAR System on July 1, 2002. Pet. 44 n.7 (citing Ex. 1058). Petitioner asserts that the SEC required companies to file their 10-K documents electronically at that time, *id.* (citing Ex. 1059), and thus, Alkermes 10-K "would have been immediately uploaded and available" for public viewing on or about July 1, 2002, *id.* (citing Ex. 1060).

Patent Owner contends that Petitioner has not established that Alkermes 10-K qualifies as a printed publication. Prelim. Resp. 48–51. Specifically, Patent Owner contends that Petitioner "fails to establish that the Alkermes 10-K was *catalogued* or *indexed* in a way that might establish public accessibility." *Id.* at 49. Patent Owner also contends that, even if the Alkermes 10-K was catalogued or indexed, Petitioner presents no evidence that an ordinarily skilled artisan "would have looked for the Alkermes 10-K or even known that it existed, let alone known how to access it." *Id.* at 50. Finally, Patent Owner contends that Petitioner "fails to authenticate the printouts" upon which it relies to show the filing date of Alkermes 10-K and past SEC protocol about EDGAR with testimony from a declarant. *Id.* We agree with Patent Owner's arguments.

Even ignoring the potential admissibility concerns with Exhibits 1058, 1059, and 1060, we also agree with Patent Owner that Petitioner's evidence does not demonstrate that an ordinarily skilled artisan—interested in preparing long-acting naltrexone formulations for the purpose of treating patients in need of naltrexone and exercising reasonable diligence—would have known to locate Alkermes 10-K. *See Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, slip. op. 21 (PTAB Oct. 6, 2017) (Paper 12) (determining that 10-K document did not qualify as a printed publication in part because "Petitioner has not explained that interested persons would have looked for the IDEC 10-K/A to gain information relating to [the at-issue] subject matter, would have known that the IDEC 10-K/A existed, or upon looking, would have been able to access the IDEC 10-K/A on [the relevant date], exercising reasonable diligence.").

2. *Reason to Combine*

Even if we considered Alkermes 10-K, we would find that Petitioner has not shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to combine the teachings of that document with Vivitrex Specimen, Rubio, and/or Wright. First, Petitioner's arguments attempting a connection between Alkerman 10-K and Vivitrex Specimen based on a "™" symbol seems to us both haphazard and tenuous. Second, we view Dr. Park's testimony on this issue conclusory and unsupported by evidence. *See, e.g.*, Ex. 1030 ¶ 129 (stating that, after reviewing Alkermes 10-K, "a next step a POSA would take is to determine what type of trademark was pending, what useful information was provided about the covered product, and if it was approved"). Dr. Park states that he "understand[s] from counsel that USPTO records are public and that the trademark specimen for Vivitrex is part of the prior art." *Id.* ¶ 130. To us, this statement appears to undermine Dr. Park's assertion that an ordinarily skilled artisan would have taken, as a "next step," a search of the USPTO's trademark files. *Id.* ¶ 29.

3. *Summary*

Notwithstanding the above, we institute *inter partes* review of all challenged claims (1–13) for obviousness over Alkermes 10-K, Vivitrex Specimen, Rubio, and Wright in light of *SAS* and the USPTO Guidance.

H. Secondary Considerations

Patent Owner presents evidence and argument relating the secondary considerations of (1) unexpected results, (2) long-felt but unsolved need, (3) industry skepticism, and (4) commercial success. *See* Prelim. Resp. 55–61. Evidence of secondary considerations "must always when present be

considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quotation omitted). But "secondary considerations are not an element of a claim of anticipation." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008). In this case, we have instituted trial based on anticipation, and thus we also institute on all obviousness grounds raised in the petition in accordance with *SAS* and USPTO Guidance. We determine that it is appropriate under these circumstances to defer review of Patent Owner's evidence and arguments about secondary considerations, given that we may not deny institution of any obviousness grounds. Any final decision on obviousness *vel non* will be based on the full record developed during the trial.

I. Discretion Under 35 U.S.C. § 325(d)

Finally, Patent Owner asserts that we should exercise our discretion to deny institution under 35 U.S.C. § 325(d) "because the same or substantially the same prior art or arguments previously were presented to the Office." Pet. 61–62 (quoting 35 U.S.C. § 325(d)).

In evaluating whether to exercise our discretion under Section 325(d), we weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner

has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, slip op. at 17–18 (Paper 8, Dec. 15, 2017) (informative).

Patent Owner does not analyze these factors, but instead asserts summarily that Comer, Kranzler, and Wright were "of record during prosecution," and that "the claims were allowed over the references." Prelim. Resp. 62. We are not persuaded that the factors weigh in favor of exercising our discretion under 35 U.S.C. § 325(d). Although Comer is listed on the face of the '499 patent, we have no evidence about the extent to which the Examiner evaluated Comer during examination. Moreover, although Kranzler and Wright are cited in the background portion of the '499 patent's written description, Patent Owner does not point us to where in the prosecution history the Examiner actually considered these references. For these reasons, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '499 patent is unpatentable. Thus, in accordance with USPTO Guidance and *SAS*, we institute an *inter partes* review of all of the challenged claims on all grounds set forth in the Petition. Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final

decision as to patentability of any claim for which *inter partes* review has been instituted. Any final decision will be based on the full record developed during trial.

V. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–13 of U.S. Patent No. 7,919,499 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '499 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

PETITIONER:

Nichole M. Valeyko
Michael H. Teschner
Tedd W. Van Buskirk
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
nvaleyko@lernerdavid.com
mteschner.ipr@ldlkm.com
tvanbuskirk@lernerdavid.com

PATENT OWNER:

Naveen Modi
Bruce M. Wexler
Michael Stramiello
Andrew Cochran
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
michaelstramiello@paulhastings.com
andrewcochran@paulhastings.com

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	Release by Secured Party (Second Lien)

CONVEYING PARTY DATA

Name	Execution Date
Morgan Stanley Senior Funding, Inc.	09/24/2012

RECEIVING PARTY DATA

Name:	Alkermes, Inc.
Street Address:	852 Winter Street
City:	Waltham
State/Country:	MASSACHUSETTS
Postal Code:	02451

Name:	Alkermes Pharma Ireland Limited
Street Address:	Monskland
City:	Athlone Co. Westmeath
State/Country:	IRELAND

Name:	Alkermes Controlled Therapeutics Inc.
Street Address:	852 Winter Street
City:	Waltham
State/Country:	MASSACHUSETTS
Postal Code:	02451

OP $16560.00 5688801

PROPERTY NUMBERS Total: 414

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CORRESPONDENCE DATA

Fax Number:

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone: 212-225-2415
Email: dilan@cgsh.com
Correspondent Name: Daniel Ilan
Address Line 1: One Liberty Plaza c/o Cleary Gottlieb
Address Line 4: New York, NEW YORK 10006

NAME OF SUBMITTER:	Megan St. Ledger
	This document serves as an Oath/Declaration (37 CFR 1.63).

Total Attachments: 39
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TERMINATION AND RELEASE OF SECURITY INTEREST IN PATENTS

This Termination and Release of Security Interest in Patents (this "**Release**") is granted on this 24th day of September, 2012, by Morgan Stanley Senior Funding, Inc. ("**Morgan Stanley**"), as collateral agent for the Secured Parties under the security agreements referenced below, in favor of Alkermes, Inc., a corporation organized under the laws of the Commonwealth of Pennsylvania, located at 852 Winter Street, Waltham, Massachusetts; Alkermes Pharma Ireland Limited, a private limited company organized under the laws of the Republic of Ireland (registered number 448848), located at Monksland, Athlone Co. Westmeath, Ireland; and Alkermes Controlled Therapeutics Inc., a corporation organized under the laws of the Commonwealth of Pennsylvania, located at 852 Winter Street, Waltham, Massachusetts (together, "**Alkermes**" or the "**Borrowers**"), with respect to the Patents (as defined below).

W I T N E S S E T H :

WHEREAS, the Borrowers and Morgan Stanley are party to a Second Lien Guarantee and Collateral Agreement dated as of September 16, 2011, in favor of Morgan Stanley;

WHEREAS, pursuant to the Second Lien Guarantee and Collateral Agreement, on September 16, 2011, Morgan Stanley, as collateral agent, and Borrowers entered into a Patent Security Agreement, which was recorded with the U.S. Patent and Trademark Office (the "**USPTO**") on September 29, 2011, at Reel/Frame 026994/0245 (the "**2011 Patent Security Agreement**");

WHEREAS, pursuant to the 2011 Patent Security Agreement, Morgan Stanley received a security interest in all of Borrowers' rights, titles and interests in the United States and throughout the world in the Patent Collateral (as this term is defined in the 2011 Patent Security Agreement), including, without limitation, those patents and patent applications set forth on Schedules A and B hereto; and

WHEREAS, Morgan Stanley desires to release any and all security interests, and any other lien, it has in the Patent Collateral to Alkermes.

NOW THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Morgan Stanley hereby agrees as follows:

1. Morgan Stanley hereby releases, terminates and discharges, without representation, recourse or warranty whatsoever, each security interest in the Patent Collateral that was granted to Morgan Stanley under the 2011 Patent Security Agreement. Morgan Stanley acknowledges and agrees that the 2011 Patent Security Agreement has been terminated.

2. The parties hereto authorize and request that (i) with respect to the Patent Collateral listed on Schedule A, the Director of Patents and Trademarks of the United States of America and (ii) with respect to the Patent Collateral listed on Schedule B, the appropriate officer in the Republic of Ireland, record this Release against the Patent Collateral. Morgan Stanley agrees to perform, at the Borrowers' expense, all further acts and execute and deliver all further documents and/or instruments that may be reasonably necessary to carry out the provisions of this Release.

3. This Release shall be governed by and construed in accordance with the law of the State of New York.

4. This Release shall be binding upon Morgan Stanley's representatives, successors, assigns and transferees.

[Remainder of Page Intentionally Blank]

IN WITNESS WHEREOF, the undersigned has caused this Release to be executed by its duly authorized representatives as of the date first above written.

MORGAN STANLEY SENIOR FUNDING, INC.

By _____
Name: Stephen B. King
Title: VP
Date: 9/24/12

STATE OF New York)
COUNTY OF New York) ss.:

On this 24th day of September 2012, before me, the undersigned, a notary public in and for said state and county, personally appeared Stephen B. King, personally known to me (or proved to me on the basis of satisfactory evidence), to be the individual who executed the foregoing instrument on behalf of _____ as the VP of such company and acknowledged to me that the execution and delivery of said instrument was duly authorized by said company.

P Morgan Stanley Senior Funding, Inc.

Julie G. Floyd
Notary Public

(Affix Seal Below)

JULIE A FLOYD
Notary Public - State of New York
NO. 01FL6134780
Qualified in New York County
Commission Expires October 3, 2015

Notary Page to
Signature to Alkermes Patent Release for September 16, 2011

SCHEDULE A

ASSIGNMENT REEL FRAME: 026994/0245

Alkermes Patent Schedule
September 2011

Case #: 000166.0051
Title: MICROENCAPSULATED 3-PIPERIDINYL-SUBSTITUTED 1,2-BENZISOXAZOLES AND 1,2-BENZISOTHIAZOLES
Owner: ALKERMES, INC. and JANSSEN PHARMACEUTICA

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	01	DIV	Granted	08/403,432	14-Mar-1995	5,688,801	18-Nov-1997	18-Nov-2014
US	03	CON	Granted	09/005,549	12-Jan-1998	5,965,168	12-Oct-1999	19-Nov-2013
US	04	CON	Granted	09/252,486	18-Feb-1999	6,110,921	29-Aug-2000	19-Nov-2013
US	05	CON	Granted	09/578,908	26-May-2000	6,368,632	09-Apr-2002	19-Nov-2013
US	06	DIV	Granted	10/058,072	29-Jan-2002	6,544,559	08-Apr-2003	19-Nov-2013
US	07	DIV	Granted	10/359,226	06-Feb-2003	6,803,055	12-Oct-2004	19-Nov-2013
US	08	DIV	Granted	10/920,422	18-Aug-2004	7,118,763	10-Oct-2006	19-Nov-2013
US	11	REX	Granted	90/007,907	26-Jan-2006	5,688,801	18-Nov-1997	18-Nov-2014
US	12	REX	Granted	90/008,151	28-Aug-2006	6,368,632	23-Oct-2007	19-Nov-2013
US	13	REX	Granted	90/008,212	12-Sep-2006	6,110,921	04-Mar-2008	19-Nov-2013
US	14	REX	Granted	90/008,216	12-Sep-2006	5,965,168	22-Apr-2008	19-Nov-2013
US	16	CON	Granted	11/826,384	13-Jul-2007	7,547,452	16-Jun-2009	19-Nov-2013

Alkermes Patent Schedule
September 2011

Case #: 000166.0053
Title: PREPARATION OF BIODEGRADABLE MICROPARTICLES CONTAINING A BIOLOGICALLY ACTIVE AGENT
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent#	Issue Date	Expiration Date
US	00	CON	Granted	08/725,439	03-Oct-1996	5,650,173	22-Jul-1997	19-Nov-2013
US	01	CON	Granted	08/729,277	10-Oct-1996	5,654,008	05-Aug-1997	19-Nov-2013

Alkermes Patent Schedule
September 2011

Case #: 000166.0063
Title: PREPARATION OF EXTENDED SHELF-LIFE BIODEGRADABLE, BIOCOMPATIBLE MICROPARTICLES CONTAINING A BIOLOGICALLY ACTIVE AGENT
Owner: ALKERMES, INC. and JANSSEN PHARMACEUTICA

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	02	ORD	Granted	08/850,679	02-May-1997	5,792,477	11-Aug-1998	02-May-2017
US	03*	CON	Granted	09/071,865	04-May-1998	5,916,598	29-Jun-1999	02-May-2017
US	04*	CON	Granted	09/263,098	05-Mar-1999	6,110,503	29-Aug-2000	02-May-2017
US	05*	CON	Granted	09/578,717	26-May-2000	6,290,983	18-Sep-2001	02-May-2017
US	06*	CON	Granted	09/920,862	03-Aug-2001	6,403,114	11-Jun-2002	02-May-2017
US	11*	REX	Granted	90/007,587	15-Jun-2005	6,110,503	02-Feb-2010	02-May-2017
US	12	REX	Granted	90/008,093	26-Jun-2006	5,792,477	13-Jul-2010	02-May-2017

NOTE: The assignment in cases noted (*) denote Alkermes, Inc. ownership only. Other cases without note, including all ex-US patents and applications, are co-owned by Alkermes and Janssen Pharmaceutica.

Alkermes Patent Schedule
September 2011

Case #: 000166.0070
Title: METHOD FOR PREPARING MICROPARTICLES HAVING A SELECTED RELEASE PROFILE
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	01	ORD	Granted	09/223,276	30-Dec-1998	6,194,006	27-Feb-2001	30-Dec-2018
US	02	CON	Granted	09/722,335	28-Nov-2000	6,379,703	30-Apr-2002	30-Dec-2018
US	03	CON	Granted	10/059,115	31-Jan-2002	6,596,316	22-Jul-2003	30-Dec-2018

Alkermes Patent Schedule
September 2011

Case #: 000166.0073
Title: PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY
Owner: ALKERMES PHARMA IRELAND LIMITED AND ALKERMES CONTROLLED THERAPEUTICS, INC.[1]

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/577,875	25-May-2000	6,495,164	17-Dec-2002	25-May-2020
US	01	CON	Granted	10/259,949	30-Sep-2002	6,667,061	23-Dec-2003	25-May-2020
US	02	DIV	Granted	10/681,142	09-Oct-2003	7,371,406	13-May-2008	25-May-2020
US	03	CON	Granted	11/826,994	19-Jul-2007	7,799,345	21-Sep-2010	25-May-2020
US	05	CON	Published	12/856,198	13-Aug-2010			

Case #: 000166.0075
Title: APPARATUS AND METHOD FOR PREPARING MICROPARTICLES
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/438,659	12-Nov-1999	6,331,317	18-Dec-2001	12-Nov-2019
US	01	CON	Granted	09/828,849	10-Apr-2001	6,395,304	28-May-2002	12-Nov-2019
US	02	CON	Granted	10/109,641	01-Apr-2002	6,537,586	25-Mar-2003	12-Nov-2019
US	03	CON	Granted	10/355,061	31-Jan-2003	6,713,090	30-Mar-2004	12-Nov-2019
US	04	CON	Granted	10/713,039	17-Nov-2003	6,861,016	01-Mar-2005	12-Nov-2019

[1] Recordation in the relevant patent office(s) to reflect ownership interest held by Alkermes Pharma Ireland Limited will occur after Close.

Case #: 000166.0077
Title: PROCESS FOR ADJUSTING POLYMER MOLECULAR WEIGHT POLYMER MICROPARTICLES
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/575,075	19-May-2000	6,264,987	24-Jul-2001	19-May-2020
US	01	CON	Granted	09/870,751	01-Jun-2001	6,379,704	30-Apr-2002	19-May-2020
US	02	CON	Granted	10/073,864	14-Feb-2002	6,534,092	18-Mar-2003	19-May-2020
US	00	ORD	Granted	09/671,426	27-Sep-2000	6,471,995	29-Oct-2002	27-Sep-2020
US	01	DIV	Granted	10/235,534	06-Sep-2002	6,830,737	14-Dec-2004	27-Sep-2020
US	02	CON	Granted	10/821,941	12-Apr-2004	6,884,372	26-Apr-2005	27-Sep-2020

Case #: 000166.0098
Title: APPARATUS AND METHOD FOR PREPARING MICROPARTICLES USING IN-LINE SOLVENT EXTRACTION
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/438,656	12-Nov-1999	6,495,166	17-Dec-2002	12-Nov-2019
US	01	DIV	Granted	09/930,450	16-Aug-2001	6,540,393	01-Apr-2003	12-Nov-2019
US	02	CON	Granted	10/319,845	16-Dec-2002	6,705,757	16-Mar-2004	12-Nov-2019
US	03	CON	Granted	10/729,909	09-Dec-2003	6,939,033	06-Sep-2005	12-Nov-2019
US	04	CON	Granted	11/158,078	22-Jun-2005	7,300,671	27-Nov-2007	12-Nov-2019
US	05	CON	Granted	11/826,533	16-Jul-2007	7,510,730	31-Mar-2009	12-Nov-2019

Case #: 000166.0106
Title: ACID END GROUP POLY(D,L-LACTIDE-CO-GLYCOLIDE) COPOLYMERS WITH HIGH GLYCOLIDE CONTENT
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/635,677	10-Aug-2000	6,362,308	26-Mar-2002	10-Aug-2020
US	01	DIV	Granted	10/060,235	01-Feb-2002	6,703,477	09-Mar-2004	10-Aug-2020
US	02	CON	Granted	10/724,107	01-Dec-2003	7,074,883	11-Jul-2006	10-Aug-2020

Alkermes Patent Schedule
September 2011

Case #: 000166.0108
Title: METHOD FOR IMPROVING MICROSPHERE FLOWABILITY CHARACTERISTICS
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	01	CIP	Granted	10/022,859	20-Dec-2001	7,247,319	24-Jul-2007	26-Jan-2023

Case #: 000166.0112
Title: RESIDUAL SOLVENT EXTRACTION METHOD AND MICROPARTICLES PRODUCED THEREBY
Owner: ALKERMES PHARMA IRELAND LIMITED[2]

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	09/942,631	31-Aug-2001	6,824,822	30-Nov-2004	31-Aug-2021
US	02	CON	Granted	11/312,371	21-Dec-2005	7,223,440	29-May-2007	31-Aug-2021
US	03	CON	Granted	11/785,638	19-Apr-2007	7,524,530	28-Apr-2009	31-Aug-2021
US	06	CON	Granted	12/382,637	20-Mar-2009	7,875,310	25-Jan-2011	31-Aug-2021
US	07	CON	Published	12/967,757	14-Dec-2010			

Case #: 000166.0118
Title: CROSSLINKED HYDROGEL COPOLYMERS
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	10/273,365	18-Oct-2002	6,800,663	05-Oct-2004	18-Oct-2022

Case #: 000166.0119
Title: METHOD AND APPARATUS FOR FILTERING AND DRYING A PRODUCT
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	00	ORD	Granted	10/304,058	26-Nov-2002	7,089,681	15-Aug-2006	26-Nov-2022

[2] Recordation in the relevant patent office(s) to reflect ownership interest held by Alkermes Pharma Ireland Limited will occur after Close.

Alkermes Patent Schedule
September 2011

Case #: 000166.0127
Title: COACERVATION PROCESS
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	12/051,395	19-Mar-2008			

Case #: 000166.0129
Title: QUENCH LIQUIDS AND WASHING SYSTEMS FOR PRODUCTION MICROPARTICLES
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Pending	12/140,542	17-Jun-2008			

Case #: 000166.0138
Title: INJECTABLE FORMULATION OF ENTECAVIR FOR TREATMENT OF HEPATITIS B
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/529,705	31-Aug-2011			

Alkermes Patent Schedule
September 2011

Case #: 000166.2025

Title: MICROENCAPSULATION AND SUSTAINED RELEASE OF BIOLOGICALLY ACTIVE POLYPEPTIDES

Owner: ALKERMES PHARMA IRELAND LIMITED[3]

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	01	ORD	Granted	10/688,786	17-Oct-2003	7,164,005	16-Jan-2007	17-Oct-2023
US	02	ORD	Granted	10/688,059	17-Oct-2003	7,462,365	09-Dec-2008	06-Feb-2025
US	04	CON	Published	12/289,857	06-Nov-2008			

[3] Recordation in the relevant patent office(s) to reflect ownership interest held by Alkermes Pharma Ireland Limited will occur after Close.

Alkermes Patent Schedule
September 2011

Case #: 000166.2056
Title: POLYMER-BASED SUSTAINED RELEASE DEVICE
Owner: ALKERMES PHARMA IRELAND LIMITED[4] and AMYLIN PHARMACEUTICALS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	01*	RCE	Granted	11/104,877	13-Apr-2005	7,456,254	25-Nov-2008	30-Jun-2025
US	03*	PCT	Pending	10/592,769	14-Sep-2006			15-Apr-2024
US	04	DIV	Granted	11/521,091	14-Sep-2006	7,563,871	21-Jul-2009	15-Apr-2024
US	09*	CON	Granted	11/826,535	16-Jul-2007	7,612,176	03-Nov-2009	13-Apr-2025
US	12	ORD	Published	11/578,712	23-Jan-2008			
US	14	CON	Published	12/483,871	12-Jun-2009			
US	15*	CON	Published	12/585,574	17-Sep-2009			
US	16*	CON	Published	12/713,036	25-Feb-2010			

NOTE: The assignment in cases noted (*) denote Alkermes, Inc. as the assignee. All other US cases are assigned to both Alkermes, Inc. and Amylin Pharmaceuticals, Inc.

[4] Recordation in the relevant patent office(s) to reflect ownership interest held by Alkermes Pharma Ireland Limited will occur after Close.

Alkermes Patent Schedule
September 2011

Case #: 4000.3000
Title: Polymorphic Forms of Naltrexone
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Granted	10/860,608	03-Jun-2004	7,279,579	09-Oct-2007	07-May-2026
US	2	DIV	Published	11/860,677	25-Sep-2007			

Case #: 4000.3002
Title: Methods for Administering Active Agent to CYP3A4 Sensitive Patients
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/241,404	30-Sep-2008			

Case #: 4000.3003
Title: Aripiprazole, Olanzapine and Haloperidol Pamoate Salts
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	10/635,232	06-Aug-2003	6,987,111	17-Jan-2006	10-May-2024

Alkermes Patent Schedule
September 2011

Case #: 4000.3005
Title: Methods for Administering Aripiprazole
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	CON	Pending	12/251,656	15-Oct-2008			

Alkermes Patent Schedule
September 2011

Case #: 4000.3010
Title: Naltrexone Long Acting Formulations and Methods of Use
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Granted	11/083,167	17-Mar-2005	7,919,499	05-Apr-2011	15-Oct-2029
US	2	DIV	Published	13/037,713	01-Mar-2011			

Alkermes Patent Schedule
September 2011

Case #: 4000.3022
Title: Selective Opioid Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	2	ORD	Published	12/371,334	13-Feb-2009			

Case #: 4000.3027
Title: Morphinan Derivatives with High Oral Bioavailability
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/727,784	19-Mar-2010			

Case #: 4000.3028
Title: Heterocyclic Compounds for the Treatment of Neurological and Psychological Disorders
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	2	ORD	Published	12/823,007	24-Jun-2010			

Alkermes Patent Schedule
September 2011

Case #: 4000.3030
Title: Asenapine Prodrugs
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	12/978,298	23-Dec-2010			

Case #: 4000.3031
Title: Quaternary Ammonium Salt Prodrugs
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/978,178	23-Dec-2010			

Alkermes Patent Schedule
September 2011

Case #: 4000.3033
Title: Prodrugs NH-Acidic Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1A	ORD	Published	12/823,102	24-Jun-2010			

Case #: 4000.3034
Title: Prodrugs Heteraromatic Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	12/978,273	23-Dec-2010			

Case #: 4000.3035
Title: Prodrugs for the Treatment of Schizophrenia and Bipolar Disease
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/978,274	23-Dec-2010			

Alkermes Patent Schedule
September 2011

Case #: 4000.3036
Title: Diaryldiazepine Prodrugs for the Treatment of Neurological and Psychological Disorders
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/978,240	23-Dec-2010			

Case #: 4000.3038
Title: Morphinan Derivatives for the Treatment of Drug Overdose
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Published	12/903,462	13-Oct-2010			

Case #: 4000.3039
Title: Process for Synthesizing Oxidized Lactam Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	13/100,515	04-May-2011			

Alkermes Patent Schedule
September 2011

Case #: 4000.3041
Title: Process for the Synthesis Substituted Morphinans
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	13/096,679	28-Apr-2011			

Case #: 4000.3042
Title: Prodrugs NH-Acidic Compounds: Carbonate, Carbamate and Phosphonate Derivatives
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	13/168,497	24-Jun-2011			

Case #: 4000.3043
Title: Methods for Treating Antipsychotic-Induced Weight Gain
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	1	ORD	Pending	13/215,718	23-Aug-2011			23-Aug-2031

Case #: 4000.3044
Title: Multi-API Loading Prodrugs
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/427,026	23-Dec-2010			23-Dec-2011

Alkermes Patent Schedule
September 2011

Case #: 4000.3047
Title: Peripherally Acting Mu Opioid Antagonists
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/442,629	14-Feb-2011			14-Feb-2012

Case #: 4000.3048
Title: Process for the Synthesis of Quaternary Amine Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/472,016	05-Apr-2011			05-Apr-2012

Case #: 4000.3051
Title: Crystalline Salt Forms of an Opioid Modulator
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/495,203	09-Jun-2011			09-Jun-2012

Alkermes Patent Schedule
September 2011

Case #: 4000.3052
Title: Peripherally Acting Opioid Compounds
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/502,721	29-Jun-2011			

Case #: 4000.3054
Title: Prodrugs of Nucleoside Analogs
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/527,986	26-Aug-2011			

Alkermes Patent Schedule
September 2011

Case #: 513352
Title: Formulations Having Improved Site Reactions
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		PRO	Pending	61/454,008	18-Mar-2011			18-Mar-2012

Alkermes Patent Schedule
September 2011

Case #: 1733.1002
Title: Composition for Sustained Release Human Growth Hormone
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	4	CON	Granted	09/505,508	17-Feb-2000	6,500,448	31-Dec-2002	02-Dec-2012

Case #: 1733.1004
Title: Composition and Method for the Controlled Release Metal Cation-Stabilized Interferon
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	08/279,784	25-Jul-1994	5,711,968	27-Jan-1998	27-Jan-2015
US	001	CON	Granted	08/765,558	07-Mar-1997	6,165,508	26-Dec-2000	26-Dec-2017
US	014	CON	Granted	10/092,365	06-Mar-2002	6,780,434	24-Aug-2004	25-Jul-2014

Case #: 1733.1009
Title: Production Scale Method Forming Microparticles
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	08/443,726	18-May-1995	5,922,253	13-Jul-1999	13-Jul-2016
US	021	CON	Granted	09/305,413	05-May-1999	6,153,129	28-Nov-2000	18-May-2015
US	022	CON	Granted	09/587,821	06-Jun-2000	6,358,443	19-Mar-2002	18-May-2015
US	023	CON	Granted[5]	10/006,991	06-Dec-2001	6,726,860	27-Apr-2004	13-Jul-2015
US	041	CON	Granted	10/784,474	23-Feb-2004	7,037,450	02-May-2006	06-Dec-2021

[5] Note: The Company has decided to abandon this registration

Case #: 1733.1015
Title: Method for Fabricating Polymer-Based Controlled-Release Devices
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	08/649,128	14-May-1996	5,817,343	06-Oct-1998	14-May-2016
US	007	CIP	Granted	08/779,777	07-Jan-1997	6,183,781	06-Feb-2001	14-May-2016

Case #: 1733.1016
Title: Composition and Method Using Solid-Phase Particles for Sustained In Vivo Release a Biologically Active Agent
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	001	ORD	Granted	08/705,197	29-Aug-1996	5,916,597	29-Jun-1999	29-Aug-2016

Case #: 1733.1018
Title: Device for the Sustained Release Aggregation-Stabilized Biologically Active Agent
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	008	CON	Granted	08/934,830	22-Sep-1997	6,514,533	04-Feb-2003	31-Aug-2015
US	011	CON	Granted	09/820,587	29-Mar-2001	6,555,525	29-Apr-2003	31-Aug-2015

Case #: 1733.1044
Title: A Method for Purifying Human Growth Hormone
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	09/260,362	01-Mar-1999	6,451,347	17-Sep-2002	01-Mar-2019

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Case #: 1733.1045
Title: Method for Producing Submicron Particles a Labile Agent and Use There
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	09/321,091	28-May-1999	6,444,223	03-Sep-2002	28-May-2019
US	007	CON	Granted	10/200,057	18-Jul-2002	6,713,087	30-Mar-2004	28-May-2019

Case #: 1733.1051
Title: Method for Producing Sub-Micron Particles Biologically Active Agents and Uses There
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	09/422,751	21-Oct-1999	6,284,283	04-Sep-2001	21-Oct-2019
US	003	CON	Granted	09/898,524	03-Jul-2001	6,428,815	06-Aug-2002	21-Oct-2019

Case #: 1733.1055
Title: Microencapsulation and Sustained Release Biologically Active Acid-Stable or Free Sulfhydryl-Containing Proteins
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	09/501,934	10-Feb-2000	6,465,425	15-Oct-2002	10-Feb-2020

Case #: 1733.1056
Title: Process for the Preparation of Polymer-Based Sustained Release Compositions
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC. AND ALKERMES PHARMA IRELAND LIMITED[6]

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	001	CON	Granted	09/801,272	07-Mar-2001	6,479,065	12-Nov-2002	10-Aug-2020

[6] Recordation in the relevant patent office(s) to reflect ownership interest held by Alkermes Pharma Ireland Limited will occur after Close.

Case #: 1733.1057
Title: Method and Apparatus for Uniform Sorbate Equilibration Solid Samples
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		ORD	Granted	09/507,238	18-Feb-2000	6,499,361	31-Dec-2002	18-Feb-2020

Case #: 1733.1062
Title: Methods and Compositions for the Targeted Delivery of Biologically Active Agents
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	003	CON	Granted	10/342,448	14-Jan-2003	7,097,857	29-Aug-2006	20-Mar-2021

Case #: 1733.1068
Title: Method of Modifying the Release Profile Sustained Release Compositions
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	008	CON	Granted	10/758,717	16-Jan-2004	7,074,432	11-Jul-2006	25-Mar-2023

Case #: 1733.1070
Title: Process for Producing Small Particles Biologically Active Molecules
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	017	FWC	Granted	08/006,682	21-Jan-1993	6,569,458	27-May-2003	27-May-2020

Case #: 1733.2012
Title: Method of Preparing Sustained Release Microparticles
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US	001	ORD	Granted	10/762,220	21-Jan-2004	7,658,998	09-Feb-2010	13-Oct-2027

Case #: 1733.2040
Title: Method of Modifying the Release Profile Sustained Release Compositions
Owner: ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		CON	Pending[7]	11/826,694	17-July-2007			

Case #: 0947.1044-031
Title: Increasing Blood-Brain Barrier Permeability with Permeabilizer Peptides
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
US		DIV	Granted	08/121,058	13-Sep-1993	5,506,206	09-Apr-1996	09-Apr-2013

[7] Note: The Company has decided to abandon this application

Country	Status	Patent Number	Application Number	Publication Number	Filing Date	Issue / Grant Date	Normal Expiry Date	Owner	Short Title / Subject Matter
USA	Granted	5260478	07/986,646		08-Dec-1992	09-Nov-1993	08-Dec-2012	Alkermes Pharma Ireland Limited	IODINATED ARCYLOXY CARBOXAMIDES
USA	Granted	5264610	08/038,371		29-Mar-1993	23-Nov-1993	29-Mar-2013	Alkermes Pharma Ireland Limited	IODINATED AROMATIC PROPANEDIOATES
USA	Granted	5328404	08/148,112		04-Nov-1993	12-Jul-1994	29-Mar-2013	Alkermes Pharma Ireland Limited	METHOD OF X-RAY IMAGING USING IODINATED AROMATIC PROPANEDIATES
USA	Granted	5298262	07/987,904		04-Dec-1992	29-Mar-1994	04-Dec-2012	Alkermes Pharma Ireland Limited	USE OF IONIC CLOUD POINT MODIFIERS TO PREVENT PARTICLE AGGREGATION DURING STERILIZATION
USA	Granted	5302401	07/987,879		09-Dec-1992	12-Apr-1994	09-Dec-2012	Alkermes Pharma Ireland Limited	METHOD TO REDUCE PARTICLE SIZE GROWTH DURING LYOPHILIZATION
USA	Granted	5451393	08/207,533		07-Mar-1994	19-Sep-1995	19-Sep-2012	Alkermes Pharma Ireland Limited	X-RAY CONTRAST COMPOSITIONS USEFUL IN MEDICAL IMAGING
USA	Granted	5322679	07/990,987		16-Dec-1992	21-Jun-1994	16-Dec-2012	Alkermes Pharma Ireland Limited	IODINATED ARCYLOXY ESTERS
USA	Granted	5466439	08/261,794		20-Jun-1994	14-Nov-1995	16-Dec-2012	Alkermes Pharma Ireland Limited	IODINATED ARCYLOXY ESTERS
USA	Granted	5326552	07/991,909		17-Dec-1992	05-Jul-1994	17-Dec-2012	Alkermes Pharma Ireland Limited	FORMULATIONS FOR NANOPARTICULATE X-RAY BLOOD POOL CONTRAST AGENTS USING HIGH
USA	Granted	5447710	08/242,492		13-May-1994	05-Sep-1995	05-Sep-2012	Alkermes Pharma Ireland Limited	METHOD OF MAKING NANOPARTICULATE X-RAY BLOOD POOL CONTRAST AGENTS USING HIGH
USA	Granted	5330739	07/985,415		04-Dec-1992	19-Jul-1994	04-Dec-2012	Alkermes Pharma Ireland Limited	IODINATED BENZOYL ACETALS AND KETALS FOR X-RAY IMAGING
USA	Granted	5470583	08/240,509		10-May-1994	28-Nov-1995	11-Dec-2012	Alkermes Pharma Ireland Limited	METHOD OF PREPARING NANOPARTICLE COMPOSITIONS CONTAINING CHARGED PHOSPHOLIPIDS TO
USA	Granted	5346688	07/991,640				16-Dec-2012	Alkermes Pharma Ireland Limited	NCD - Diagnostic Imaging
USA	Granted	5346702	07/985,424		04-Dec-1992	13-Sep-1994	04-Dec-2012	Alkermes Pharma Ireland Limited	USE OF NON-IONIC CLOUD POINT MODIFIERS TO MINIMIZE NANOPARTICLE AGGREGATION DURING
USA	Granted	5362459	07/991,639		16-Dec-1992	04-Oct-1994	16-Dec-2012	Alkermes Pharma Ireland Limited	USE OF PURIFIED SURFACE MODIFIERS TO PREVENT PARTICLE AGGREGATION DURING STERILIZATION
USA	Granted	5384107	08/285,595		03-Aug-1994	24-Jan-1995	14-Dec-2012	Alkermes Pharma Ireland Limited	IODINATED AROMATIC COMPOUNDS
USA	Granted	5494683	08/365,267		28-Dec-1994	27-Feb-1996	27-Feb-2013	Alkermes Pharma Ireland Limited	SURFACE MODIFIED ANTICANCER NANOPARTICLES
USA	Granted	5401492	07/981,893		17-Dec-1992	28-Mar-1995	17-Dec-2012	Alkermes Pharma Ireland Limited	WATER INSOLUBLE NON-MAGNETIC MANGANESE PARTICLES AS MAGNETIC RESONANCE CONTRACT
USA	Granted	5429824	07/990,874		15-Dec-1992	04-Jul-1995	15-Dec-2012	Alkermes Pharma Ireland Limited	USE OF TYLOXAPOL AS A NANOPARTICLE STABILIZER AND DISPERSANT
USA	Granted	5466440	08/367,407		30-Dec-1994	14-Nov-1995	30-Dec-2014	Alkermes Pharma Ireland Limited	FORMULATIONS OF ORAL GASTROINTESTINAL DIAGNOSTIC X-RAY CONTRAST AGENTS IN COMBINATION
USA	Granted	5643552	08/524,145		22-Aug-1995	01-Jul-1997	22-Aug-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE DIAGNOSTIC MIXED CARBONIC ANHYDRIDES AS X-RAY CONTRAST AGENTS FOR
USA	Granted	5472683	08/401,570		09-Mar-1995	05-Dec-1995	09-Mar-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE DIAGNOSTIC MIXED CARBAMIC ANHYDRIDES AS X-RAY CONTRAST AGENTS FOR
USA	Granted	5573749	08/401,397		09-Mar-1995	12-Nov-1996	09-Mar-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE DIAGNOSTIC MIXED CARBOXYLIC ANHYDRIDES AS X-RAY CONTRAST AGENTS FOR
USA	Granted	5488133	08/209,181		10-Mar-1994	30-Jan-1996	10-Mar-2014	Alkermes Pharma Ireland Limited	IODINATED ARCYLOXY KETONES
USA	Granted	5500204	08/366,788		10-Feb-1995	19-Mar-1996	10-Feb-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE DIAGNOSTIC DIMERS AS X-RAY CONTRAST AGENTS FOR BLOOD POOL AND
USA	Granted	5503723	08/385,531		08-Feb-1995	02-Apr-1996	08-Feb-2015	Alkermes Pharma Ireland Limited	ISOLATION OF ULTRA SMALL PARTICLES
USA	Granted	5510118	08/388,092		14-Feb-1995	23-Apr-1996	14-Feb-2015	Alkermes Pharma Ireland Limited	PROCESS OF PREPARING THERAPEUTIC COMPOSITIONS CONTAINING NANOPARTICLES
USA	Granted	5518187	08/180,827		12-Jan-1994	21-May-1996	12-Jan-2014	Alkermes Pharma Ireland Limited	METHOD OF GRINDING PHARMACEUTICAL SUBSTANCES
USA	Granted	5518738	08/385,614		09-Feb-1995	21-May-1996	09-Feb-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE NSAID COMPOSITIONS
USA	Granted	5521218	08/440,794		15-May-1995	28-May-1996	15-May-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE IODIPAMIDE DERIVATIVES FOR USE AS X-RAY CONTRAST AGENTS
USA	Granted	5525328	08/265,550		24-Jun-1994	11-Jun-1996	24-Jun-2014	Alkermes Pharma Ireland Limited	NANOPARTICULATE DIAGNOSTIC DIATRIZOXY ESTER X-RAY CONTRAST AGENTS FOR BLOOD POOL AND
USA	Granted	5534270	08/386,028		09-Feb-1995	09-Jul-1996	09-Feb-2015	Alkermes Pharma Ireland Limited	METHOD OF PREPARING STABLE DRUG NANOPARTICLES
USA	Granted	5543133	08/388,099		14-Feb-1995	06-Aug-1996	14-Feb-2015	Alkermes Pharma Ireland Limited	PROCESS OF PREPARING X-RAY CONTRAST COMPOSITIONS CONTAINING NANOPARTICLES
USA	Granted	5571536	08/384,057		06-Feb-1995	05-Nov-1996	06-Feb-2015	Alkermes Pharma Ireland Limited	FORMULATIONS OF COMPOUNDS AS NANOPARTICULATE DISPERSIONS IN DIGESTIBLE OILS OR FATTY
USA	Granted	5560931	08/388,088		14-Feb-1995	01-Oct-1996	14-Feb-2015	Alkermes Pharma Ireland Limited	FORMULATIONS OF COMPOUNDS AS NANOPARTICULATE DISPERSIONS IN DIGESTIBLE OILS OR FATTY
USA	Granted	5560932	08/370,955		10-Jan-1995	01-Oct-1996	10-Jan-2015	Alkermes Pharma Ireland Limited	MICROPRECIPITATION OF NANOPARTICULATE PHARMACEUTICAL AGENTS
USA	Granted	5565188	08/393,972		24-Feb-1995	15-Oct-1996	24-Feb-2015	Alkermes Pharma Ireland Limited	POLYALKYLENE BLOCK COPOLYMERS AS SURFACE MODIFIERS FOR NANOPARTICLES
USA	Granted	5705194	08/727,883		08-Oct-1996	06-Jan-1998	24-Feb-2015	Alkermes Pharma Ireland Limited	POLYALKYLENE BLOCK COPOLYMERS AS SURFACE MODIFIERS FOR NANOPARTICLES
USA	Granted	5569448	08/378,022		24-Jan-1995	29-Oct-1996	24-Jan-2015	Alkermes Pharma Ireland Limited	SULFATED NONIONIC BLOCK COPOLYMER SURFACTANTS AS STABILIZER COATINGS FOR NANOPARTICLE
USA	Granted	5573750	08/447,133		22-May-1995	12-Nov-1996	22-May-2015	Alkermes Pharma Ireland Limited	DIAGNOSTIC IMAGING X-RAY CONTRAST AGENTS
USA	Granted	5573783	08/387,651		13-Feb-1995	12-Nov-1996	13-Feb-2015	Alkermes Pharma Ireland Limited	REDISPERSIBLE NANOPARTICULATE FILM MATRICES WITH PROTECTIVE OVERCOATS
USA	Granted	5580579	08/388,878		15-Feb-1995	03-Dec-1996	15-Feb-2015	Alkermes Pharma Ireland Limited	SITE-SPECIFIC ADHESION WITHIN THE GI TRACT USING NANOPARTICLES STABILIZED BY HIGH
USA	Granted	5585108	08/366,518		30-Dec-1994	17-Dec-1996	30-Dec-2014	Alkermes Pharma Ireland Limited	FORMULATIONS OF ORAL GASTROINTESTINAL THERAPEUTIC AGENTS IN COMBINATION WITH
USA	Granted	5587143	08/267,082		28-Jun-1994	24-Dec-1996	28-Jun-2014	Alkermes Pharma Ireland Limited	BUTYLENE OXIDE-ETHYLENE OXIDE BLOCK COPOLYMER SURFACTANTS A S STABILIZER COATINGS FOR
USA	GRANTED	5591456	08/386,790		10-Feb-1995	07-Jan-1997	10-Feb-2015	Alkermes Pharma Ireland Limited	MILLED NAPROXEN WITH HYDROXYPROPYL CELLULOSE AS A DISPERSION STABILIZER
USA	Granted	5593657	08/386,027		09-Feb-1995	14-Jan-1997	09-Feb-2015	Alkermes Pharma Ireland Limited	NOVEL BARIUM SALT FORMULATIONS STABILIZED BY NON-IONIC AND ANIONIC STABILIZERS
USA	Granted	5603916	08/447,132		22-May-1995	18-Feb-1997	22-May-2015	Alkermes Pharma Ireland Limited	3 5-BIS ALKANOYL AMINO-2 4 6-TRIIODOBENZYL ESTERS
USA	Granted	5622938	08/444,796		19-May-1995	22-Apr-1997	09-Feb-2015	Alkermes Pharma Ireland Limited	SUGAR BASE SURFACTANT FOR NANOCRYSTALS
USA	Granted	5628981	08/366,841		30-Dec-1994	13-May-1997	30-Dec-2014	Alkermes Pharma Ireland Limited	FORMULATIONS OF ORAL GASTROINTESTINAL DIAGNOSTIC X-RAY CONTRAST AGENTS AND ORAL
USA	Granted	6,432,381 B2	08/815,346	US 2001-0006617 A1	11-Mar-1997	13-Aug-2002	30-Dec-2014	Alkermes Pharma Ireland Limited	METHODS FOR TARGETING DRUG DELIVERY TO THE UPPER AND/OR LOWER GASTROINTESTINAL TRACT
USA	Published		10/175,851	US 2003-0054045 A1	21-Jun-2002		30-Dec-2014	Alkermes Pharma Ireland Limited	METHODS FOR TARGETING DRUG DELIVERY TO THE UPPER AND/OR LOWER GASTROINTESTINAL TRACT
USA	Granted	5662883	08/370,936		10-Jan-1995	02-Sep-1997	10-Jan-2015	Alkermes Pharma Ireland Limited	MICROPRECIPITATION OF MICRO-NANOPARTICULATE PHARMACEUTICAL AGENTS
USA	Granted	5665331	08/370,998		10-Jan-1995	09-Sep-1997	10-Jan-2015	Alkermes Pharma Ireland Limited	CO-MICROPRECIPITATION OF NANOPARTICULATE PHARMACEUTICAL AGENTS WITH CRYSTAL GROWTH
USA	Granted	5868196	08/677,709		10-Jul-1996	16-Sep-1997	10-Jul-2016	Alkermes Pharma Ireland Limited	NOVEL 3-AMIDO-TRIIODOPHENYL ESTERS AS X-RAY CONTRAST AGENTS
USA	Granted	5870138	08/586,363		16-Jan-1996	23-Sep-1997	23-Sep-2014	Alkermes Pharma Ireland Limited	2,4,6-TRIIODO-5-SUBSTITUTED-AMINOISOPHTHALATE ESTERS USEFUL AS X-RAY CONTRAST AGENTS FOR
USA	GRANTED	5716642	08/370,928		10-Jan-1995	10-Feb-1998	10-Feb-2015	Alkermes Pharma Ireland Limited	MICROPRECIPITATION OF NANOPARTICULATE PHARMACEUTICAL AGENTS USING SURFACE ACTIVE
USA	GRANTED	5718388	08/249,787		25-May-1994	17-Feb-1998	17-Feb-2015	Alkermes Pharma Ireland Limited	CONTINUOUS METHOD OF GRINDING PHARMACEUTICAL SUBSTANCES
USA	Granted	5718919	08/393,648		25-May-1994	17-Feb-1998	17-Feb-2015	Alkermes Pharma Ireland Limited	NANOPARTICLES CONTAINING THE R(-)ENANTIOMER OF IBUPROFEN
USA	Granted	5747001	08/393,573		24-Feb-1995	05-May-1998	05-May-2015	Alkermes Pharma Ireland Limited	AEROSOLS CONTAINING BECLOMETHAZONE NANOPARTICLE DISPERSIONS
USA	Granted	5834025	08/696,754		14-Aug-1996	10-Nov-1998	14-Aug-2016	Alkermes Pharma Ireland Limited	REDUCTION OF INTRAVENOUSLY ADMINISTERED NANOPARTICULATE-FORMULATION-INDUCED ADVERSE
USA	Granted	RE41,884 E	12/027,100		06-Feb-2008	26-Oct-2010	14-Aug-2016	Alkermes Pharma Ireland Limited	REDUCTION OF INTRAVENOUSLY ADMINISTERED NANOPARTICULATE-FORMULATION-INDUCED ADVERSE
USA	Granted	5862999	08/491,539		15-Jun-1995	26-Jan-1999	25-May-2014	Alkermes Pharma Ireland Limited	METHOD OF GRINDING PHARMACEUTICAL SUBSTANCES
USA	Granted	5936030	08/836,819		14-Aug-1997	10-Aug-1999	10-Aug-2016	Alkermes Pharma Ireland Limited	POLYETHER COPOLYMERS AND A PROCESS FOR PREPARING THEM
USA	GRANTED	6045829	08/890,602		09-Jul-1997	04-Apr-2000	13-Feb-2017	Alkermes Pharma Ireland Limited	NANOCRYSTALLINE FORMULATIONS OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) PROTEASE INHIBITORS
USA	Granted	6068858	09/225,498		06-Jan-1999	30-May-2000	09-Jul-2017	Alkermes Pharma Ireland Limited	METHODS OF MAKING NANOCRYSTALLINE FORMULATIONS OF HUMAN IMMUNODEFICIENCY VIRUS (HIV)
USA	Granted	6221400	09/225,498		06-Jan-1999	24-Apr-2001	13-Feb-2017	Alkermes Pharma Ireland Limited	METHODS OF TREATING MAMMALS USING NANOCRYSTALLINE FORMULATIONS OF HUMAN
USA	GRANTED	6153225	09/154,422		13-Aug-1998	28-Nov-2000	13-Aug-2018	Alkermes Pharma Ireland Limited	INJECTABLE FORMULATIONS OF NANOPARTICULATE NAPROXEN
USA	Granted	6165506	09/148,332		04-Sep-1998	26-Dec-2000	04-Sep-2018	Alkermes Pharma Ireland Limited	NEW SOLID DOSE FORM OF NANOPARTICULATE NAPROXEN
USA	Granted	6264922	08/948,216		09-Oct-1997	24-Jul-2001	24-Feb-2015	Alkermes Pharma Ireland Limited	NEBULIZED AEROSOLS CONTAINING NANOPARTICULATE DISPERSIONS
USA	Pending		09/577,489		22-May-2000		24-Feb-2015	Alkermes Pharma Ireland Limited	METHODS OF ADMINISTRATING LIQUID DROPLET AEROSOLS OF NANOPARTICULATE DRUGS
USA	APPEAL		12/081,670	US 2008-0274044 A1	18-Apr-2008		24-Feb-2015	Alkermes Pharma Ireland Limited	METHODS OF ADMINISTRATING LIQUID DROPLET AEROSOLS OF NANOPARTICULATE DRUGS
USA	Granted	7,521,068 B2	09/190,138	US 2002-0102294 A1	12-Nov-1998	21-Apr-2009	12-Apr-2022	Alkermes Pharma Ireland Limited	DRY POWDER AEROSOLS OF NANOPARTICULATE DRUGS
USA	Granted	6811767	09/587,736		19-Jun-2000	02-Nov-2004	12-Nov-2018	Alkermes Pharma Ireland Limited	LIQUID DROPLET AEROSOLS OF NANOPARTICULATE DRUGS
USA	Published		12/320,431	US 2009-0181100 A1	26-Jan-2009		12-Nov-2018	Alkermes Pharma Ireland Limited	LIQUID DROPLET AEROSOLS OF NANOPARTCULATE DRUGS
USA	GRANTED	6270806	09/261,151		03-Mar-1999	07-Aug-2001	03-Mar-2019	Alkermes Pharma Ireland Limited	USE OF PEG-DERIVATIZED LIPIDS AS SURFACE STABILIZERS FOR NANOPARTICULATE COMPOSITIONS
USA	GRANTED	6267989	09/263,834		08-Mar-1999	31-Jul-2001	08-Mar-2019	Alkermes Pharma Ireland Limited	METHODS FOR PREVENTING CRYSTAL GROWTH AND PARTICLE AGGREGATION IN NANOPARTICULATE
USA	Granted	6656504	09/392,557		09-Sep-1999	02-Dec-2003	09-Sep-2019	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS COMPRISING AMORPHOUS CYCLOSPROINE AND METHODS OF
USA	Published		09/337,675	US 2002-0012675 A1	22-Jun-1999		01-Oct-2018	Alkermes Pharma Ireland Limited	CONTROLLED-RELEASE NANOPARTICULATE COMPOSITIONS
USA	APPEAL		11/979,231	US 2008-0124393 A1	31-Oct-2007		01-Oct-2018	Alkermes Pharma Ireland Limited	CONTROLLED-RELEASE NANOPARTICULATE CLOZAPINE COMPOSITIONS
USA	Published		12/483,188	US 2009-0297619 A1	11-Jun-2009		22-Jun-2019	Alkermes Pharma Ireland Limited	NANOPARTICULATE ANTICONVULSANT AND IMMUNOSUPPRESSIVE COMPOSITIONS

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Country	Status	Patent Number	Application Number	Publication Number	Filing Date	Issue / Grant Date	Normal Expiry Date	Owner	Short Title / Subject Matter
USA	Pending		13/102,795		06-May-2011		01-Oct-2018	Alkermes Pharma Ireland Limited	CONTROLLED-RELEASE NANOPARTICULATE CLOZAPINE COMPOSITIONS
USA	Granted	6428814	09/414,159	US 2002-0068092 A1	08-Oct-1999	06-Aug-2002	08-Oct-2019	Alkermes Pharma Ireland Limited	BIOADHESIVE NANOPARTICULATE COMPOSITIONS HAVING CATIONIC SURFACE STABILIZERS
USA	Granted	7282267	10/004,808	US 2003-0108611 A1	08-Oct-1999	30-Oct-2007	23-May-2021	Alkermes Pharma Ireland Limited	BIOADHESIVE NANOPARTICULATE COMPOSITIONS HAVING CATIONIC SURFACE STABILIZERS
USA	Granted	7850995	11/898,274	US 2008 0003295 A1	11-Sep-2007	14-Dec-2010	08-Oct-2019	Alkermes Pharma Ireland Limited	BIOADHESIVE NANOPARTICULATE COMPOSITIONS HAVING CATIONIC SURFACE STABILIZERS
USA	Granted	6431478	09/583,893		31-May-2000	13-Aug-2002	26-Jul-2020	Alkermes Pharma Ireland Limited	SMALL-SCALE MILL AND METHOD THEREOF
USA	Granted	6745962	10/037,586	US 2002-0145062 A1	19-Oct-2001	08-Jun-2004	31-May-2020	Alkermes Pharma Ireland Limited	SMALL-SCALE MILL AND METHOD THEREOF
USA	Granted	6991191	10/833,045	US 2004-0251332 A1	28-Apr-2004	31-Jan-2006	30-Jun-2020	Alkermes Pharma Ireland Limited	SMALL-SCALE MILL AND METHOD THEREOF
USA	Granted	6316029	09/572,961		18-May-2000	13-Nov-2001	18-May-2020	Alkermes Pharma Ireland Limited	RAPID-DISINTEGRATING SOLID ORAL DOSAGE FORM
USA	Published		10/667,470	US 2004-0057993 A1	23-Sep-2003		18-May-2020	Alkermes Pharma Ireland Limited	RAPID-DISINTEGRATING SOLID ORAL DOSAGE FORM
USA	Published		12/068,706	US 2008-0213371 A1	11-Feb-2008		18-May-2020	Alkermes Pharma Ireland Limited	RAPID-DISINTEGRATING SOLID ORAL DOSAGE FORM
USA	Granted	6375986	09/666,539		21-Sep-2000	23-Apr-2002	21-Sep-2020	Alkermes Pharma Ireland Limited	SOLID DOSE NANOPARTICULATE COMPOSITIONS COMPRISING A SYNERGISTIC COMBINATION OF A
USA	Granted	6592903	10/075,443	US 2002-0110597 A1	15-Feb-2002	15-Jul-2003	21-Sep-2020	Alkermes Pharma Ireland Limited	SOLID DOSE NANOPARTICULATE COMPOSITIONS COMPRISING A SYNERGISTIC COMBINATION OF A
USA	Granted	6969529	10/345,512	US 2003-0180616 A1	16-Jan-2003	29-Nov-2005	21-Sep-2020	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS COMPRISING COPOLYMERS OF VINYL PYRROLIDONE AND VINY
USA	Granted	7244451	11/213,765	US 2007-0141159 A1	30-Aug-2005	17-Jul-2007	05-Feb-2021	Alkermes Pharma Ireland Limited	METHODS OF MAKING NANOPARTICULATE DRUG COMPOSITIONS COMPRISING COPOLYMERS OF VINY
USA	Granted	6582285	09/842,619	US 2001-0053664 A1	26-Apr-2001	24-Jun-2003	26-Apr-2021	Alkermes Pharma Ireland Limited	APPARATUS FOR SANITARY WET MILLING
USA	APPEAL		10/246,751	US 2003-0095928 A1	19-Sep-2002		19-Sep-2022	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF INSULIN
USA	Granted	6742734	10/162,333	US 2002-0179758 A1	04-Jun-2002	01-Jun-2004	06-Aug-2022	Alkermes Pharma Ireland Limited	SYSTEM AND METHOD FOR MILLING MATERIALS
USA	Granted	6976647	10/732,801	US 2004-0164194 A1	11-Dec-2003	20-Dec-2005	04-Jun-2022	Alkermes Pharma Ireland Limited	SYSTEM AND METHOD FOR MILLING MATERIALS
USA	Granted	7575184	11/833,845	US 2008-0029807 A1	03-Aug-2007	18-Aug-2009	04-Aug-2022	Alkermes Pharma Ireland Limited	SYSTEM AND METHOD FOR MILLING MATERIALS
USA	APPEAL		09/952,032	US 2003-0054042 A1	14-Sep-2001		14-Sep-2021	Alkermes Pharma Ireland Limited	STABILIZATION OF CHEMICAL COMPOUNDS USING NANOPARTICULATE FORMULATIONS
USA	APPEAL		11/802,158	US 2007-0224279 A1	21-May-2007		14-Sep-2021	Alkermes Pharma Ireland Limited	STABILIZATION OF CHEMICAL COMPOUNDS USING NANOPARTICULATE FORMULATIONS
USA	Pending		11/979,251		31-Oct-2007		14-Sep-2021	Alkermes Pharma Ireland Limited	STABILIZATION OF CHEMICAL COMPOUNDS USING NANOPARTICULATE FORMULATIONS
USA	Published		12/121,443	US 2009-0175951 A1	15-May-2008		14-Sep-2021	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF IMMUNOSUPPRESSIVE AGENTS
USA	Granted	7459283	10/357,514	US 2003-0185869 A1	04-Feb-2003	02-Dec-2008	10-Jul-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS HAVING LYSOZYME AS A SURFACE STABILIZER
USA	Published		12/282,091	US 2009-0074875 A1	12-Nov-2008		04-Feb-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS HAVING LYSOZYME AS A SURFACE STABILIZER
USA	APPEAL		11/275,069	US 2006-0153920 A1	07-Dec-2005		21-Sep-2020	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF MAP KINASE INHIBITORS
USA	APPEAL		10/035,324	US 2003-0129242 A1	04-Jan-2002		04-Jan-2022	Alkermes Pharma Ireland Limited	STERILE FILTERED NANOPARTICULATE FORMULATIONS OF BUDESONIDE AND BECLOMETHASONE
USA	Granted	7713551	10/659,706	US 2005-0031691 A1	11-Sep-2003	11-May-2010	12-Nov-2024	Alkermes Pharma Ireland Limited	GEL-STABILIZED NANOPARTICULATE ACTIVE AGENT COMPOSITIONS
USA	APPEAL		11/928,250	US 2008-0050461 A1	30-Oct-2007		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	APPEAL		11/928,278	US 2008-0107741 A1	30-Oct-2007		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	APPEAL		11/928,289	US 2008-0226732 A1	30-Oct-2007		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Published		12/076,247	US 2008-0220075 A1	14-Mar-2008		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Published		12/117,982	US 2008-0279949 A1	09-May-2008		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Published		12/870,722	US 2010-0322852 A1	27-Aug-2010		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Published		12/870,745	US 2010- 0322853	27-Aug-2010		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Published		12/870,749	US 2010-0329976 A1	27-Aug-2010		20-Mar-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS OF ANGIOGENESIS INHIBITORS
USA	Granted	7101576	10/412,669	US 2003-0219490 A1	14-Apr-2003	05-Sep-2006	12-Apr-2024	Alkermes Pharma Ireland Limited	NANOPARTICULATE MEGESTROL FORMULATIONS
USA	Published		10/878,623	US 2005-0008707 A1	29-Jun-2004		14-Apr-2023	Alkermes Pharma Ireland Limited	NANPARTICULATE MEGESTROL FORMULATIONS
USA	APPEAL		11/093,149	US 2005-0233001 A1	30-Mar-2005		14-Apr-2023	Alkermes Pharma Ireland Limited	NANPARTICULATE MEGESTROL FORMULATIONS
USA	APPEAL		11/472,556	US 2010-0226889 A1	22-Jun-2006			Alkermes Pharma Ireland Limited	NANOPARTICULATE MEGESTROL FORMULATIONS
USA	Published		12/826,557	US 2010-0266705 A1	29-Jun-2010		14-Apr-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE MEGESTROL FORMULATIONS
USA	Granted	7276249	10/444,096	US 2005-0276874 A1	23-May-2003	02-Oct-2007	21-Feb-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE FIBRATE FORMULATIONS
USA	Granted	7320802	10/692,855	US 2004-0058009 A1	27-Oct-2003	22-Jan-2008	21-Feb-2023	Alkermes Pharma Ireland Limited	METHODS OF TREATMENT USING NANOPARTICULATE FENOFIBRATE COMPOSITIONS
USA	APPEAL		11/710,607	US 2007-0264348 A1	26-Feb-2007		21-Feb-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE FIBRATE FORMULATIONS
USA	Allowed		11/802,542	US 2007-0298115 A1	23-May-2007		21-Feb-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE FIBRATE FORMULATIONS
USA	APPEAL		11/802,567	US 2008-0095851 A1	23-May-2007		21-Feb-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE FIBRATE FORMULATIONS
USA	Published		11/979,230	US 2008-0138424-A1	31-Oct-2007		21-Feb-2023	APIL & Fournier	NANOPARTICULATE FIBRATE FORMULATIONS
USA	Published		12/058,497	US 2008-0241070 A1	28-Mar-2008		21-Feb-2023	APIL & Fournier	NANOPARTICULATE FIBRATE FORMULATIONS
USA	Published		11/367,716	US 2011-0027371 A1	06-Mar-2006		01-Oct-2018	Alkermes Pharma Ireland Limited	NANOPARTICULATE STATIN FORMULATIONS & NOVEL STATIN COMBINATIONS
USA	Granted	7,763,278 B2	10/457,811	US 2003-0232796 A1	10-Jun-2003	27-Jul-2010	03-Mar-2024	Alkermes Pharma Ireland Limited	NANOPARTICULATE POLYCOSANOL FORMULATIONS AND NOVEL POLYCOSANOL COMBINATIONS
USA	Published		12/704,426	US 2010-0143962 A1	11-Feb-2010		10-Jun-2023	Alkermes Pharma Ireland Limited	NANOPARTICULATE POLYCOSANOL FORMULATIONS AND NOVEL POLYCOSANOL COMBINATIONS
USA	PENDING		10/784,900	US 2004-0229038 A1	24-Feb-2004		24-Feb-2024	Alkermes Pharma Ireland Limited	NANOPARTICULATE MELOXICAM FORMULATIONS
USA	Published		12/788,208	US 2010-0297252 A1	26-May-2010		24-Feb-2024	Alkermes Pharma Ireland Limited	NANOPARTICULATE MELOXICAM FORMULATIONS
USA	Published		10/705,227	US 2004-0156895 A1	12-Nov-2003		12-Nov-2023	Alkermes Pharma Ireland Limited	SOLID DOSAGE FORMS COMPRISING PULLULAN
USA	APPEAL		10/619,539	US 2004-0258757 A1	16-Jul-2003		16-Jul-2023	Alkermes Pharma Ireland Limited	LIQUID DOSAGE COMPOSITIONS OF STABLE NANOPARTICULATE ACTIVE AGENTS
USA	Pending		13/044,450		09-Mar-2011			Alkermes Pharma Ireland Limited	LIQUID DOSAGE COMPOSITIONS OF STABLE NANOPARTICULATE ACTIVE AGENTS
USA	APPEAL		10/654,600	US 2004-0105778 A1	04-Sep-2003		04-Sep-2023	Alkermes Pharma Ireland Limited	GAMMA IRRADIATION OF SOLID NANOPARTICULATE ACTIVE AGENTS
USA	Granted	7,198,795 B2	10/323,736	US 2004-0029099 A1	20-Dec-2002	03-Apr-2007	07-Jan-2021	Alkermes Pharma Ireland Limited	IN VITRO METHODS FOR EVALUATING THE IN VIVO EFFECTIVENESS OF DOSAGE FORMS OF
USA	Granted	7695739	11/650,412		06-Jan-2007		21-Sep-2020	Alkermes Pharma Ireland Limited	IN VITRO METHODS FOR EVALUATING THE IN VIVO EFFECTIVENESS OF DOSAGE FORMS OF
USA	Published		12/729,018	US 2010-0178648 A1	22-Mar-2010		21-Sep-2020	Alkermes Pharma Ireland Limited	IN VITRO METHODS FOR EVALUATING THE IN VIVO EFFECTIVENESS OF DOSAGE FORMS OF
USA	Granted	7390505	10/766,960	US 2004-0258758 A1	30-Jan-2004	24-Jun-2008	30-Jan-2024	Alkermes Pharma Ireland Limited	NANOPARTICULATE TOPIRAMATE FORMULATIONS
USA	Pending		13/189,299		22-Jul-2011		2/2/2024	Alkermes Pharma Ireland Limited	NOVEL FLUTICASONE FORMULATIONS
USA	Published		10/420,527	US 2004-0105889 A1	23-Apr-2003		14-Apr-2023	Alkermes Pharma Ireland Limited	LOW VISCOSITY LIQUID DOSAGE FORMS
USA	APPEAL		11/979,253	US 2008-0152585 A1	31-Oct-2007		14-Apr-2023	Alkermes Pharma Ireland Limited	LOW VISCOSITY LIQUID DOSAGE FORMS
USA	Granted	7842232	10/851,681	US 2010-0255102 A1	24-May-2004	30-Nov-2010	23-Jun-2027	Alkermes Pharma Ireland Limited	STERILIZATION OF DISPERSIONS OF NANOPARTICULATE ACTIVE AGENTS WITH GAMMA RADIATION
USA	APPEAL		10/895,405	US 2005-0042177 A1	21-Jul-2004			Alkermes Pharma Ireland Limited	NOVEL COMPOSITIONS OF SILDENAFIL FREE BASE
USA	APPEAL		10/697,709	US 2004-0156872 A1	31-Oct-2003			Alkermes Pharma Ireland Limited	NOVEL NIMESULIDE COMPOSITIONS
USA	Pending		13/183,545		28-Jul-2011		5/18/2021	Alkermes Pharma Ireland Limited	NOVEL NIMESULIDE COMPOSITIONS
USA	Published		12/282,092	US 2009-0074873 A1	12-Nov-2008		24-Feb-2015	Alkermes Pharma Ireland Limited	NANOPARTICULATE BECLOMETHASONE DIPROPRIONATE COMPOSITIONS
USA	APPEAL		10/687,716	US 2004-0141925 A1	31-Oct-2003		16-Jul-2023	Alkermes Pharma Ireland Limited	NOVEL TRIAMCINOLONE COMPOSITIONS
USA	APPEAL		10/701,064	US 2005-0019412 A1	05-Nov-2003			Alkermes Pharma Ireland Limited	NOVEL GLIPIZIDE COMPOSITIONS
USA	Published		10/712,259	US 2004-0115134 A1	14-Nov-2003		22-Jun-2019	Alkermes Pharma Ireland Limited	NOVEL NIFEDIPINE COMPOSITIONS
USA	Published		11/980,720	US 2008-0047209 A1	31-Oct-2007		22-Jun-2019	Alkermes Pharma Ireland Limited	NOVEL NIFEDIPINE COMPOSITIONS
USA	Published		12/292,395	US 2009-0104273 A1	18-Nov-2008		22-Jun-2019	Alkermes Pharma Ireland Limited	NOVEL NIFEDIPINE COMPOSITIONS
USA	Published		10/677,857	US 2004-0101596 A1	03-Oct-2003			Alkermes Pharma Ireland Limited	NOVEL BENZOYL PEROXIDE COMPOSITIONS
USA	Granted	7879360	10/978,695	US 2005-0238725 A1	02-Nov-2004	01-Feb-2011	20-Feb-2028	Alkermes Pharma Ireland Limited	NANOPARTICULATE COMPOSITIONS HAVING A PEPTIDE AS A SURFACE STABILIZER
USA	Published		10/979,792	US 2005-0147664 A1	03-Nov-2004		03-Nov-2024	Alkermes Pharma Ireland Limited	COMPOSITIONS COMPRISING ANTIBODIES AND METHODS OF USING THE SAME FOR TARGETED
USA	Granted	7910577	11/274,887	US 2006-0154918 A1	16-Nov-2005	22-Mar-2011	26-Jan-2029	Alkermes Pharma Ireland Limited	INJECTABLE FORMULATIONS OF NANOPARTICULATE OLANZAPINE
USA	Pending		12/933,233		12-Nov-2008		16-Nov-2025	Alkermes Pharma Ireland Limited	NANOPARTICULATE FORMULATIONS OF OLANZAPINE ESTERS
USA	Pending		13/024,315		09-Feb-2011		16-Nov-2025	Alkermes Pharma Ireland Limited	NANOPARTICULATE FORMULATIONS OF OLANZAPINE ESTERS

Country	Status	Patent Number	Application Number	Publication Number	Filing Date	Issue / Grant Date	Normal Expiry Date	Owner	Short Title / Subject Matter
USA	APPEAL		12/232,895	US 2009-0093366 A1	25-Sep-2008			Alkermes Pharma Ireland Limited	NANOPARTICULATE BENZOTHIOPHENE FORMULATIONS
USA	Pending		11/633,088		04-Dec-2006		04-Dec-2026	Alkermes Pharma Ireland Limited	NOVEL MOMETASONE COMPOSITIONS AND METHODS OF MAKING AND USING THE SAME
USA	APPEAL		11/377,650	US 2006-0210639 A1	17-Mar-2006		17-Mar-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE BISPHOSPHONATE COMPOSITIONS
USA	Published		11/376,554	US 2006-0210638 A1	16-Mar-2006		16-Mar-2026	Alkermes Pharma Ireland Limited	INJECTABLE COMPOSITIONS OF NANOPARTICULATE IMMUNOSUPPRESSIVE COMPOUNDS
USA	Published		11/387,068	US 2006-0216353 A1	23-Mar-2006		23-Mar-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE CORTICOSTEROID AND ANTIHISTAMINE FORMULATIONS
USA	APPEAL		11/402,264		12-Apr-2006		12-Apr-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE QUINAZOLINE DERIVATIVE FORMULATIONS
USA	APPEAL		11/402,257	US 2006-0246141 A1	12-Apr-2006		12-Apr-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE LIPASE INHIBITOR FORMULATIONS
USA	APPEAL		11/436,887		19-May-2006		19-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE INTEGRIN ANTAGONIST FORMULATIONS
USA	APPEAL		11/980,719		31-Oct-2007		19-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE INTEGRIN ANTAGONIST FORMULATIONS
USA	APPEAL		11/437,833	US 2010-0028439-A1	22-May-2006		22-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE STABILIZED ANTI-HYPERTENSIVE COMPOSITIONS
USA	Published		12/052,436	US 2008-0220074 A1	20-Mar-2008		04-Sep-2023	Alkermes Pharma Ireland Limited	GAMMA RADIATION STERILIZED NANOPARTICULATE DOCETAXEL COMPOSITIONS AND METHOD OF
USA	APPEAL		11/363,266	US 2007-0202180 A1	28-Feb-2006		28-Feb-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE CARVEDILOL FORMULATIONS
USA	Published		11/275,775	US 2007-0178051 A1	27-Jan-2006			Alkermes Pharma Ireland Limited	STERILIZED NANOPARTICULATE GLUCOCORTICOSTEROID FORMULATIONS
USA	Published		12/071,849	US 2008-0152720 A1	27-Feb-2008		15-Dec-2025	Alkermes Pharma Ireland Limited	NANOPARTICULATE TACROLIMUS FORMULATIONS
USA	Published		12/484,073	US 2009-0252806 A1	12-Jun-2009		15-Dec-2025	Alkermes Pharma Ireland Limited	NANOPARTICULATE TACROLIMUS FORMULATIONS
USA	Pending		13/039,249		02-Mar-2011		21-Dec-2025	Alkermes Pharma Ireland Limited	NANOPARTICULATE BICALUTAMIDE FORMULATIONS
USA	APPEAL		11/361,055	US 2006-0188566 A1	24-Feb-2006		24-Feb-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE FORMULATIONS OF DOCETAXEL AND ANALOGUES THEREOF
USA	Published		11/354,249	US 2006-0198896 A1	15-Feb-2006			Alkermes Pharma Ireland Limited	AEROSOL AND INJECTABLE FORMULATIONS OF NANOPARTICULATE BENZODIAZEPINE
USA	Published		12/544,197	US 2009-0304801 A1	19-Aug-2009		15-Feb-2026	Alkermes Pharma Ireland Limited	AEROSOL AND INJECTABLE FORMULATIONS OF NANOPARTICULATE BENZODIAZEPINE
USA	Published		11/325,626	US 2006-0165806 A1	05-Jan-2006			Alkermes Pharma Ireland Limited	NANOPARTICULATE CANDESARTAN FORMULATIONS
USA	APPEAL		11/372,227	US 2006-0204588 A1	10-Mar-2006		10-Mar-2026	Alkermes Pharma Ireland Limited	FORMULATIONS OF A NANOPARTICULATE FINASTERIDE, DUTASTERIDE OR TAMSULOSIN
USA	APPEAL		11/446,589	US 2007-0042049 A1	05-Jun-2006		05-Jun-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE BENIDIPINE COMPOSITIONS
USA	APPEAL		11/446,564	US 2006-0292214 A1	05-Jun-2006		05-Jun-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE ACETAMINOPHEN FORMULATIONS
USA	Published		11/446,565	US 2006-0275372 A1	05-Jun-2006		05-Jun-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE IMATINIB MESYLATE FORMULATIONS
USA	APPEAL		11/448,984	US 2007-0059371 A1	08-Jun-2006		08-Jun-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE EBASTINE FORMULATIONS
USA	Pending		11/802,427		22-May-2007		22-May-2027	Alkermes Pharma Ireland Limited	NANOPARTICULATE POSACONAZOLE FORMULATIONS
USA	APPEAL		11/481,257		06-Jul-2006		06-Jul-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE CLARITHROMYCIN FORMULATIONS
USA	Published		11/520,059	US 2007-0104792 A1	13-Sep-2006		13-Sep-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE TADALAFIL FORMULATIONS
USA	Published		11/520,058	US 2007-0148100 A1	13-Sep-2006		13-Sep-2026	Alkermes Pharma Ireland Limited	INJECTABLE FORMULATIONS OF NANOPARTICULATE ARIPIPRAZOLE
USA	Pending		11/761,900		12-Jun-2007		12-Jun-2027	Alkermes Pharma Ireland Limited	NANOPARTICULATE KINASE INHIBITOR FORMULATIONS
USA	APPEAL		11/775,002	US 2008-0213374 A1	09-Jul-2007		09-Jul-2027	Alkermes Pharma Ireland Limited	NANOPARTICULATE FORMULATIONS OF SORAFENIB TOSYLATE
USA	Pending		11/129,807		16-May-2005		16-May-2025	Alkermes Pharma Ireland Limited	NANOPARTICLE DISPERSION CONTAINING LACTAM COMPOUND
USA	Pending		12/331,052		09-Dec-2008		09-Dec-2028	Alkermes Pharma Ireland Limited	NANOPARTICULATE ANIDULAFUNGIN COMPOSITIONS AND METHODS FOR MAKING THE SAME
USA	Published		12/329,566	2009-0311335 A1	24-Feb-2009		24-Feb-2029	Alkermes Pharma Ireland Limited	COMBINATION OF A TRIPTAN AND AN NSAID
USA	Pending		13/110,647		18-May-2011		18-May-2031	Alkermes Pharma Ireland Limited	NANOPARTICULATE CINACALCET COMPOSITIONS
USA	APPEAL		11/262,672		31-Oct-2005		31-Oct-2025	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING A COMBINATION OF ISOSORBIDE DINITRATE AND
USA	Published		11/373,629	US 2007-0098791 A1	10-Mar-2006		31-Oct-2025	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING A COMBINATION OF ISOSORBIDE DINITRATE AND
USA	Published		11/569,483	US 2008-0268043 A1	01-Feb-2008		26-Jan-2026	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING AN ANTIPSYCHOTIC AGENT
USA	Published		11/329,893	US 2006-0269596 A1	11-Jan-2006		11-Jan-2026	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING AN ACYLANILIDE
USA	Pending		11/568,841		29-Jun-2007		14-Feb-2026	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING LEVETIRACETAM
USA	Pending		11/571,379		12-Apr-2006		12-Apr-2026	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING A CEPHALOSPORIN FOR THE TREATMENT OF A
USA	APPEAL		11/558,202	US 2007-0122481 A1	09-Nov-2006		01-Nov-2019	Alkermes Pharma Ireland Limited	MODIFIED RELEASE COMPOSITIONS COMPRISING A FLUOROCYTIDINE DERIVATIVE FOR THE TREATMENT
USA	Pending		11/568,925		16-Nov-2006		01-Nov-2019	Alkermes Pharma Ireland Limited	MODIFIED RELEASE LOXOPROFEN COMPOSITIONS
USA	Published		11/422,226	US 2006-0118556 A1	05-Jun-2006		01-Nov-2019	Alkermes Pharma Ireland Limited	MODIFIED RELEASE OF COMPOSITIONS CONTAINING A COMBINATION OF CARBIDOPA, LEVODOPA AND
USA	Granted	5505962	08/307,392		16-Sep-1994	09-Apr-1996	09-Apr-2013	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE PHARMACEUTICAL FORMULATION
USA	Granted	5641745	08/479,509		07-Jun-1995	24-Jun-1997	07-Jun-2015	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE BIODEGRADABLE MICRO- AND NANOSPHERES CONTAINING CYCLOSPORIN
USA	Granted	5964620	07/921,459		28-Jul-1992	15-Nov-1994	15-Nov-2011	Alkermes Pharma Ireland Limited	CONTROLLED ABSORPTION DILTIAZEM FORMULATION FOR ONCE-DAILY ADMINISTRATION
USA	Granted	5616345	08/334,864		04-Nov-1994	01-Apr-1997	01-Apr-2014	Alkermes Pharma Ireland Limited	CONTROLLED ABSORPTION DILTIAZEM FORMULATION FOR ONCE-DAILY ADMINISTRATION
USA	Granted	5336504	08/064,401		19-May-1993	09-Aug-1994	22-Jul-2012	Alkermes Pharma Ireland Limited	DILTIAZEM FORMULATION AND METHODS OF TREATMENT
USA	Licensed	5370879	08/078,651		07-Jun-1993	06-Dec-1994	06-Dec-2011	Alkermes Pharma Ireland Limited	FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES
USA	Licensed	5540938	08/328,185		24-Oct-1994	30-Jul-1996	30-Jul-2013	Alkermes Pharma Ireland Limited	FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES
USA	Licensed	5580580	08/479,506		07-Jun-1995	03-Dec-1996	03-Dec-2013	Alkermes Pharma Ireland Limited	FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES
USA	Licensed	5533995	08/244,094		13-May-1994	09-Jul-1996	09-Jul-2013	Alkermes Pharma Ireland Limited	PASSIVE TRANSDERMAL DEVICE WITH CONTROLLED DRUG DELIVERY
USA	Licensed	6068339	08/977,965		25-Nov-1997	23-May-2000	25-Nov-2017	Alkermes Pharma Ireland Limited	ORAL MORPHINE MULTIPARTICULATE FORMULATION
USA	Licensed	6228398	09/566,636		08-May-2000	08-May-2001	01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION
USA	Licensed	6730325	09/850,425	US 2002-0054907 A1	07-May-2001	04-May-2004	01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYPHENIDATE
USA	Licensed	6902742	10/331,754	US 2003-0129237 A1	30-Dec-2002	07-Jun-2005	01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYPHENIDATE
USA	Licensed	6793936	10/354,483	US 2003-0170304 A1	30-Jan-2003	21-Sep-2004	01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYPHENIDATE
USA	APPEAL		10/827,689	US 2004-0197405 A1	19-Apr-2004		01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYPHENIDATE
USA	Published		11/372,857	US 2006-0240105 A1	10-Mar-2006		01-Nov-2019	Alkermes Pharma Ireland Limited	MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYPHENIDATE
USA	Granted	7465462	09/744,169		19-Apr-2001	16-Dec-2008	10-May-2020	Alkermes Pharma Ireland Limited	MULTIPARTICULATE CONTROLLED RELEASE SELECTIVE SEROTININ REUPTAKE INHIBITOR FORMULATIONS
USA	Granted	7021168	10/492,098	US 2005-0003550 A1	08-Apr-2004	04-Apr-2006	09-Oct-2022	Alkermes Pharma Ireland Limited	APPARATUS AND METHOD FOR CONCURRENTLY MONITORING ACTIVE RELEASE AND PHYSICAL
USA	Pending		12/626,001	US 2010-0272807	25-Nov-2009			Alkermes Pharma Ireland Limited	SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS
USA	Pending		12/626,085	US 2010-0272796	25-Nov-2009			Alkermes Pharma Ireland Limited	SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS
USA	Pending		12/626,036	US 2010-0272795	25-Nov-2009			Alkermes Pharma Ireland Limited	SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS
USA	Published		11/568,891	US 2010-0136106 A1	15-Jan-2010		07-Jun-2026	Alkermes Pharma Ireland Limited	MODIFIED RELEASE FAMCICLOVIR COMPOSITIONS
USA	Published		11/569,481	US 2009-0297597 A1	21-Nov-2006			Alkermes Pharma Ireland Limited	MODIFIED RELEASE TICLOPIDINE COMPOSITIONS
USA	Pending		13/044,225		09-Mar-2011			Alkermes Pharma Ireland Limited	ALCOHOL RESISTANT ENTERIC PHARMACEUTICAL COMPOSITIONS
United States	Granted	US 5,841,745	08/479,509				2-Apr-2016	Alkermes Pharma Ireland Limited	CR BIODEGRADABLE MICRO- AND NANOSPHERES CONTAINING CYCLOSPORIN
USA	Granted	6908626	10/268,928	US 2003-0137067 A1	11-Oct-2002	21-Jun-2005	25-Dec-2022	Alkermes Pharma Ireland Limited	COMPOSITONS HAVING A COMBINATION OF IMMEDIATE RELEASE AND CONTROLLED RELEASE
USA	Pending		12/407,684		19-Mar-2009		19-Mar-2029	Alkermes Pharma Ireland Limited	COMPOSITIONS FOR SITE-SPECIFIC DELIVERY OF IMATINIB MESYLATE AND METHODS OF USE
USA	Published		11/297,737	US 2006-0121112 A1	08-Dec-2005		08-Dec-2025	Alkermes Pharma Ireland Limited	TOPIRAMATE PHARMACEUTICAL COMPOSITION
USA	Pending		11/571,377		14-Jan-2008		02-Mar-2026	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE COMPOSITIONS COMPRISING HETEROCYCLIC AMIDE DERIVATIVE
USA	Pending		11/568,698		03-Nov-2006		13-Apr-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING PROSTAGLANDIN
USA	Pending		11/569,206		16-Nov-2006		09-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING VITAMIN K2
USA	Published		11/568,825	US 2009-0269400 A1	11-May-2009		16-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING A CEPHALOSPORIN
USA	Published		11/568,835	US 2009-0297596 A1	23-May-2006		23-May-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING A PLATELET
USA	Granted	5641515	08/474,161		07-Jun-1995	24-Jun-1997	07-Jun-2015	Alkermes Pharma Ireland Limited	CONTROLLED RELEASE BIODEGRADABLE NANOPARTICLES CONTAINING INSULIN
USA	Pending		11/671,276		06-Feb-2007		06-Feb-2027	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING CEFDITOREN
USA	Published		11/672,283	US 2011-0008435 A1	07-Feb-2007			Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING ARYL-HETEROCYCLIC

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Country	Status	Patent Number	Application Number	Publication Number	Filing Date	Issue / Grant Date	Normal Expiry Date	Owner	Short Title / Subject Matter
USA	Published		11/479,013	US 2010-0247636 A1	30-Jun-2006		30-Jun-2026	Alkermes Pharma Ireland Limited	NANOPARTICULATE AND CONTROLLED RELEASE COMPOSITIONS COMPRISING NILVADIPINE
USA	Published		11/776,770	US 2008-0317843 A1	12-Jul-2007		12-Jul-2027	Alkermes Pharma Ireland Limited	NANOPARTICULATE FORMULATIONS OF MODAFINIL
USA	Published		12/049,046	US 2008-0226734 A1	14-Mar-2008		14-Mar-2028	Alkermes Pharma Ireland Limited	COMBINATION OF A NARCOTIC AND NON-NARCOTIC ANALGESIC
USA	Published		11/768,154	US 2008-0113025 A1	25-Jun-2007		25-Jun-2027	Alkermes Pharma Ireland Limited	COMPOSITIONS COMPRISING NANOPARTICULATE NAPROXEN AND CONTROLLED RELEASE
USA	Published		11/768,169	US 2008-0102121 A1	25-Jun-2007		25-Jun-2027	Alkermes Pharma Ireland Limited	COMPOSITIONS COMPRISING NANOPARTICULATE MELOXICAM AND CONTROLLED RELEASE
USA	Granted	5332113	07/758,364		10-Sep-1991	26-Sep-1994	26-Sep-2011	Alkermes Pharma Ireland Limited	CAP ASSEMBLY
USA	Published		10/528,727	US 2006-0104909 A1	05-Dec-2005		23-Sep-2023	APIL & VERION INC	ABUSE-RESISTENT PHARMACEUTICAL COMPOSITIONS
USA	Pending		12/757,005		08-Apr-2010			Alkermes Pharma Ireland Limited	DRUG DELIVERY COMPOSITION (NANO OSMOTIC PUMP)
USA	Pending		12/757,024		08-Apr-2010			Alkermes Pharma Ireland Limited	CONTROLLED-RELEASE CLOZAPINE COMPOSITIONS
USA	Published		12/209,726	2009-0149479 A1	12-Sep-2008		12-Sep-2028	Alkermes Pharma Ireland Limited	DOSING REGIMEN
USA	Pending		12/887,924		04-Mar-2009		04-Mar-2029	Alkermes Pharma Ireland Limited	STABLE LIQUID FORMULATIONS OF ANTI-INFECTIVE AGENTS AND ADJUSTED ANTI-INFECTIVE AGENT
USA	Published		12/788,196	US 2010-0316725 A1	26-May-2010		26-May-2030	Alkermes Pharma Ireland Limited	REDUCTION OF FLAKE-LIKE AGGREGATION IN NANOPARTICULATE ACTIVE AGENT COMPOSITIONS
USA	Granted	5242406	07/809,195		16-Dec-1991	07-Sep-1993	16-Dec-2011	Alkermes Pharma Ireland Limited	DEVICE & METHOD FOR DISPENSING A LIQUID PARTICULARLY USEFUL FOR DELIVERING MEDICAMENTS
USA	Granted	5359632	07/759,006		12-Sep-1991	18-Oct-1994	18-Oct-2011	Alkermes Pharma Ireland Limited	TRANSDERMAL DRUG DELIVERY DEVICE
USA	Granted	5380272	08/077,146		16-Jun-1993	10-Jan-1995	16-Jun-2013	Alkermes Pharma Ireland Limited	TRANSCUTANEOUS DRUG DELIVERY APPLICATOR
United States	Granted	US 5871125	08/687,692				5-Sep-2016	Alkermes Pharma Ireland Limited	Liquid delivery pumping device
USA	Granted	6312409	09/331,648		07-Sep-1999	06-Nov-2001	07-Sep-2019	Alkermes Pharma Ireland Limited	DEVICE FOR GENERATING A PULSATILE FLUID DRUG FLOW
USA	Granted	6078842	997404		23-Dec-1997	20-Jun-2000	23-Dec-2017	Alkermes Pharma Ireland Limited	IMPROVED ELECTRODE AND IONTOPHORETIC DEVICE AND METHOD
USA	Granted	6157858	08/997,388		23-Dec-1997	05-Dec-2000	23-Dec-2017	Alkermes Pharma Ireland Limited	DEVICE FOR THE DELIVERY OF A SUBSTANCE TO A SUBJECT AND IMPROVED ELECTRODE ASSEMBLY.
USA	Granted	6317630	09/239,934		29-Jan-1999	13-Nov-2001	29-Jan-2019	Alkermes Pharma Ireland Limited	DRUG DELIVERY DEVICE
USA	Granted	D454,194 S	29/135,976		23-Jan-2001	05-Mar-2002	05-Mar-2016	Alkermes Pharma Ireland Limited	DRUG RECONSTITUTION AND INJECTION DEVICE
USA	Granted	6719719	09/863,539	US 2002-0004643 A1	23-May-2001	13-Apr-2004	23-May-2021	Alkermes Pharma Ireland Limited	SPIKE FOR LIQUID TRANSFER DEVICE, LIQUID TRANSFER DEVICE INCLUDING SPIKE AND METHOD OF
USA	Licensed	5527288	08/183,482		18-Jan-1994	18-Jun-1996	18-Jan-2014	Alkermes Pharma Ireland Limited	INTRADERMAL DRUG DELIVERY DEVICE
USA	Licensed	5997501	08/647,954		19-Aug-1996	07-Dec-1999	07-Dec-2016	Alkermes Pharma Ireland Limited	INTRADERMAL DRUG DELIVERY DEVICE
USA	Licensed	5814020	08/708,230		06-Sep-1996	29-Sep-1998	06-Sep-2016	Alkermes Pharma Ireland Limited	MEDICAMENT DELIVERY DEVICE
USA	Licensed	5858001	08/763,311		10-Dec-1996	12-Jan-1999	10-Dec-2016	Alkermes Pharma Ireland Limited	CARTRIDGE-BASED DRUG DELIVERY DEVICE
USA	Licensed	6261272	09/202,176		01-Jun-1999	17-Jul-2001	04-Jun-2017	Alkermes Pharma Ireland Limited	NEEDLE FOR SUBCUTANEOUS DELIVERY OF FLUIDS
USA	Licensed	6346095	09/778,332		06-Feb-2001	12-Feb-2002	04-Jun-2017	Alkermes Pharma Ireland Limited	NEEDLE AND METHOD FOR DELIVERY OF FLUIDS
USA	Licensed	6530900	09/577,033		23-May-2000	11-Mar-2003	05-May-2018	Alkermes Pharma Ireland Limited	SUBCUTANEOUS DRUG DELIVERY DEVICE WITH IMPROVED FILLING SYSTEM
USA	Licensed	6186982	09/072,675		05-May-1998	13-Feb-2001	05-May-2018	Alkermes Pharma Ireland Limited	SUBCUTANEOUS DRUG DELIVERY DEVICE WITH IMPROVED FILLING SYSTEM
USA	Licensed	6500150	09/103,716		23-Jun-1998	31-Dec-2002	12-Feb-2019	Alkermes Pharma Ireland Limited	PRE-FILLED DRUG-DELIVERY DEVICE AND METHOD OF MANUFACTURE AND ASSEMBLY OF SAME
USA	Licensed	6824529	09/836,105	US 2002-0010423 A1	17-Apr-2001	30-Nov-2004	17-Apr-2021	Alkermes Pharma Ireland Limited	PRE-FILLED DRUG-DELIVERY DEVICE AND METHOD OF MANUFACTURE AND ASSEMBLY OF SAME
USA	Licensed	6843782	09/836,984	US 2001-0025168 A1	18-Apr-2001	18-Jan-2005	07-Oct-2018	Alkermes Pharma Ireland Limited	PRE-FILLED DRUG-DELIVERY DEVICE AND METHOD OF MANUFACTURE AND ASSEMBLY OF SAME
USA	Licensed	6275717	09/102,840		23-Jun-1998	14-Aug-2001	23-Jun-2018	Alkermes Pharma Ireland Limited	METHODS OF CALIBRATING AND TESTING A SENSOR FOR IN VIVO MEASUREMENT OF AN ANALYTE AND
USA	Licensed	6000548	09/102,841		23-Jun-1998	14-Dec-1999	23-Jun-2018	Alkermes Pharma Ireland Limited	DRUG DELIVERY KIT AND METHOD OF PACKAGING THE SAME
USA	Licensed	6585707	09/315,629	US 2001-0056262 A1	20-May-1999	01-Jul-2003	20-May-2019	Alkermes Pharma Ireland Limited	IMPROVED ADHESIVE SYSTEM FOR MEDICAL DEVICES
USA	Licensed	6595956	09/275,464		23-Mar-1999	22-Jul-2003	23-Mar-2019	Alkermes Pharma Ireland Limited	IMPROVED DRUG DELIVERY DEVICE
USA	Licensed	7364418	10/461,040	US 2003-0236498 A1	13-Jun-2003	10-Jun-2008	23-Mar-2019	Alkermes Pharma Ireland Limited	DEVICE FOR MEASURING VOLUME OF DRUG
USA	Licensed		12/121,545		15-May-2008		23-Mar-2019	Alkermes Pharma Ireland Limited	IMPROVED DRUG DELIVERY DEVICE
USA	Licensed		13/184,479		15-Jul-2011			Alkermes Pharma Ireland Limited	IMPROVED DRUG DELIVERY DEVICE
USA	Licensed		13/184,473		15-Jul-2011			Alkermes Pharma Ireland Limited	IMPROVED DRUG DELIVERY DEVICE
USA	Licensed	6520941	09/415,961		12-Oct-1999	18-Feb-2003	12-Oct-2019	Alkermes Pharma Ireland Limited	METHOD AND DEVICE FOR ENTRAPPING GAS WITHIN A LIQUID DRUG CONTAINER
USA	Licensed	7530964	09/883,025		17-Jun-2001	12-May-2009	03-Oct-2023	Alkermes Pharma Ireland Limited	NEEDLE DEVICE AND METHOD AND OPERATION THEREOF
USA	Licensed	6572740	08/832,179	27068	11-Apr-2001	03-Jun-2003	11-Apr-2021	Alkermes Pharma Ireland Limited	ELECTROLYTIC CELL
USA	Granted	6759057	07/323,182		13-Mar-1989	06-Jul-2004	06-Jul-2021	Alkermes Pharma Ireland Limited	METHODS AND COMPOSITIONS USING LIPOSOME-ENCAPSULATED NON-STEROIDAL ANTI-INFLAMMATORY
USA	Granted	5948441	08/367,923		03-Jan-1995	07-Sep-1999	07-Sep-2016	Alkermes Pharma Ireland Limited	METHOD FOR SIZE SEPARATION OF PARTICLES
USA	Granted	5626873	08/442,080		16-May-1995	06-May-1997	16-May-2015	Alkermes Pharma Ireland Limited	NOVEL EMULSIONS
USA	Granted	5525232	08/137,371		14-Oct-1993	11-Jun-1996	14-Oct-2013	Alkermes Pharma Ireland Limited	METHOD FOR ENTRAPMENT OF CATIONIC SPECIES IN LAMELLAR VESICLES
USA	Granted	5716626	08/699,869		12-Feb-1996	10-Feb-1998	12-Feb-2016	Alkermes Pharma Ireland Limited	METHOD OF SEPARATING MATERIALS FROM LIPOSOMES OR LIPID COMPLEXES
USA	Granted	5662930	08/438,665		04-May-1995	02-Sep-1997	04-May-2015	Alkermes Pharma Ireland Limited	REDUCTION OF LIPOSOME INDUCED ADVERSE PHYSIOLOGICAL REACTIONS
USA	Granted	5614214	08/247,053		20-May-1994	25-Mar-1997	20-May-2014	Alkermes Pharma Ireland Limited	REDUCTION OF LIPOSOME INDUCED ADVERSE PHYSIOLOGICAL REACTIONS
USA	Granted	5,591,123	08/381,141				07-Jan-2014	Alkermes Pharma Ireland Limited	Programmable control mounting system for transdermal drug applicator
USA	Granted	5,358,483	07/949,721				25-Oct-2011	Alkermes Pharma Ireland Limited	Disposable transdermal drug applicator
USA	Granted	5,372,579	08/204,784				13-Dec-2011	Alkermes Pharma Ireland Limited	Pulsating transdermal drug delivery syster

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SCHEDULE B

Alkermes Irish Patent Schedule
September 2011

Case #: 000166.0051
Title: MICROENCAPSULATED 3-PIPERIDINYL-SUBSTITUTED 1,2-BENZISOXAZOLES AND 1,2-BENZISOTHIAZOLES
Owner: ALKERMES, INC. and JANSSEN PHARMACEUTICA

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland		EPO	Granted	95900721.2	11-Nov-1994	0729357	2-Feb-2005	11-Nov-2014

Case #: 000166.0053
Title: PREPARATION OF BIODEGRADABLE MICROPARTICLES CONTAINING A BIOLOGICALLY ACTIVE AGENT
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent#	Issue Date	Expiration Date
Ireland	02	PCT	Granted	95 901 961.3	18-Nov-1994	0729353	06-Feb-2002	18-Nov-2014

Case #: 000166.0063
Title: PREPARATION OF EXTENDED SHELF-LIFE BIODEGRADABLE, BIOCOMPATIBLE MICROPARTICLES CONTAINING A BIOLOGICALLY ACTIVE AGENT
Owner: ALKERMES, INC. and JANSSEN PHARMACEUTICA

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland		EPO/DIV	Granted	02075905.6	06-May-1997	1210942	21-Mar-2007	6-May-2017
Ireland		EPO	Granted	97923063.8	06-May-1997	0904063	4-Sep-2002	6-May-2017

Case #: 000166.0070
Title: METHOD FOR PREPARING MICROPARTICLES HAVING A SELECTED RELEASE PROFILE
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland	00	EPP	Granted	99965212.6	10-Dec-1999	1140029	09-Nov-2005	10-Dec-2019

Case #: 000166.0073
Title: PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY
Owner: ALKERMES PHARMA IRELAND LIMITED AND ALKERMES CONTROLLED THERAPEUTICS, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland	00	EPP	Granted	01928628.5	19-Apr-2001	1283699	06-Jun-2007	19-Apr-2021

Case #: 000166.0075
Title: APPARATUS AND METHOD FOR PREPARING MICROPARTICLES
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland	00	EPP	Granted	00991722.0	03-Nov-2000	1231898	27-Dec-2006	03-Nov-2020

Case #: 000166.0077
Title: PROCESS FOR ADJUSTING POLYMER MOLECULAR WEIGHT POLYMER MICROPARTICLES
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland	00	EPP	Granted	01928630.1	19-Apr-2001	1282404	02-Jul-2008	19-Apr-2021

Case #: 000166.0098
Title: APPARATUS AND METHOD FOR PREPARING MICROPARTICLES USING IN-LINE SOLVENT EXTRACTION
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland	00	EPP	Granted	00990484.8	03-Nov-2000	1242053	12-Jan-2005	03-Nov-2020

Case #: 4000.3005
Title: Methods for Administering Aripiprazole
Owner: ALKERMES, INC.

Country	Sub Case	Case Type	Status	Application #	Filing Date	Patent #	Issue Date	Expiration Date
Ireland		EPP	Granted	04779411.0	29-Jul-2004	1660037	31-Aug-2011	29-Jul-2024

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	04/05/2011	7919499	4000.3010 US1	8002

38421 7590 03/16/2011

Elmore Patent Law Group
484 Groton Road
Westford, MA 01886

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 1673 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Elliot Ehrich, Lincoln, MA;

RT B - FEE(S) TRANSMITTAL

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P.O. Box 1450
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38421 7590 12/01/2010

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Amy Green	(Depositor's name)
	(Signature)
March 1, 2011	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

TITLE OF INVENTION: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	03/01/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
CARTER, KENDRA D	1627	514-282000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
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☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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1 Elmore Patent Law Group, P.C.
2
3 Carolyn S. Elmore
Darlene A. Vanstone

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AlKermes, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Waltham, Massachusetts

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 502807 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Darlene Vanstone Date March 1, 2011

Typed or printed name Darlene A. Vanstone Registration No. 35,729

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	11083167
Filing Date:	17-Mar-2005
Title of Invention:	NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE
First Named Inventor/Applicant Name:	Elliot Ehrich
Filer:	Darlene Vanstone/Amy Green
Attorney Docket Number:	4000.3010 US1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1810**

Electronic Acknowledgement Receipt

EFS ID:	9558169
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Amy Green
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	01-MAR-2011
Filing Date:	17-MAR-2005
Time Stamp:	14:50:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1810
RAM confirmation Number	1092
Deposit Account	502807
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	40003010US1IssueFee.pdf	161575 b55743f1a5df2bc61f29d4b8e5bb6f9fefdfb db8	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	31939 7eed7711a79717c64fcc2b7319f8e310d58a c11d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	193514		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

38421 7590 12/01/2010

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 12/01/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

TITLE OF INVENTION: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	03/01/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

38421 7590 12/01/2010

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

TITLE OF INVENTION: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	03/01/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
CARTER, KENDRA D	1627	514-282000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1_____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2_____ 3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

38421 7590 12/01/2010

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 12/01/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 899 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 899 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	11/083,167	EHRICH, ELLIOT	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *20 October 2010*.

2. ☒ The allowed claim(s) is/are *1, 6-8, 11, 13-20, 23 and 26 (renumbered 1-15)*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/29/05
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Kendra D Carter/
Examiner, Art Unit 1627

DETAILED ACTION

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Darlene Vanstone on November 19, 2010.

The application has been amended as follows:

1. In claim 1, line 2, after "formulation comprising" **insert** "about 310 mg to about 480 mg of"; and in line 3 after "naltrexone is" **delete** "at least".

2. Cancel claims 2-5.

3. In claim 6, line 2, after "naltrexone" **delete** "in a dosage between about 160 mg to about 480 mg naltrexone".

4. Cancel claims 9 and 10.

5. In claim 11, line 1, after “claim” **delete** “10” and **insert** "26".

6. Cancel claim 12.

7. In claim 13, line 2, after “naltrexone”, **insert** “wherein the serum AUC is about 3.3 times greater than that achieved by 50 mg/day oral administration”.

8. In claim 26, line 2, after “formulation comprising” **insert** “about 190 mg to about 240 mg of”; and in line 3 after "naltrexone is" **delete** "at least".

EXAMINER’S STATEMENT OF REASONS FOR ALLOWANCE

Applicant’s amendments to the claims and arguments filed October 20, 2010 has been fully considered. In light of the Applicant’s amendments and Examiner’s amendments, claims 1, 6-8, 11, 13-20, 23 and 26 are allowed and renumbered to claims 1-15.

In light of the amendment to the claims and unexpected results, the 35 U.S.C. 112, first paragraph rejection is withdrawn.

The following is an examiner's statement of reasons for allowance: The claims 1, 6-8, 11, 13-20, 23 and 26 are drawn to a method for treating an individual in need of naltrexone comprising parenterally administering a long acting formulation comprising about 310 to about 480 mg of naltrexone and polylactide-co-glycolide polymer wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration. There is no prior art disclosing the applicant's composition and effect, particularly an AUC about three times greater than that achieved by 50 mg/day oral administration. The closest art is Tice et al. (6,306,425 B1). Tice et al. teach muscular injectable naltrexone microsphere compositions and their use in reducing consumption of heroin and alcohol (see title and abstract; addresses claims 18 and 20). The composition comprises a matrix consisting of the polymer poly-(D,L-lactide) The naltrexone is released in a controlled manner for greater than 28 or about 32 days. The microsphere formulation was reported to be comparable whether taking daily 50 mg tablets for one month or one 300 mg microencapsulated naltrexone by intramuscular injection once monthly (see column 14, lines 59-64). Since the Applicant's have demonstrated in a declaration filed October 5, 2009 in Exhibit C, the claimed invention demonstrates the claimed properties over those of Tice et al. the invention is allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kendra D Carter/
Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11083167	EHRICH, ELLIOT
	Examiner	**Art Unit**
	KENDRA D CARTER	1627

ORIGINAL		INTERNATIONAL CLASSIFICATION																	
CLASS	SUBCLASS	CLAIMED										NON-CLAIMED							
514	282	A	6	1	K	31 / 44 (2006.01.01)													
CROSS REFERENCE(S)		A	0	1	N	43 / 42 (2006.01.01)													
		A	0	1	N	45 / 00 (2006.01.01)													
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)	A	6	1	K	31 / 56 (2006.01.01)													
514	171	A	6	1	F	13 / 00 (2006.01.01)													
424	422																		

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	9	17												
	2	10	18												
	3	11	19												
	4	12	20												
	5		21												
2	6		22												
3	7	13	23												
4	8		24												
	9		25												
	10	14	26												
15	11														
	12														
5	13														
6	14														
7	15														
8	16														

/KENDRA D CARTER/ Examiner.Art Unit 1627	11/19/10	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/SREENI PADMANABHAN/ Supervisory Patent Examiner.Art Unit 1627	11/20/2010	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11083167	EHRICH, ELLIOT
	Examiner	Art Unit
	KENDRA D CARTER	1617

SEARCHED

Class	Subclass	Date	Examiner
514	282,171	11/15/10	KDC
424	422	11/15/10	KDC

SEARCH NOTES

Search Notes	Date	Examiner
Inventor search (eDAN)	4/29/09	KDC
EAST (search included)	4/29/09	KDC
Google (search terms similar to EAST search)	4/29/09	KDC
Search updated	12/9/09	KDC
Search updated	7/6/10	KDC
Search updated	11/15/10	KDC
Patentability conference (Sreeni Padmanabhan, Johann Richter)	11/17/10	KDC

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
514	282,171	11/15/10	KDC
424	422	11/15/10	KDC

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 8002

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/083,167	03/17/2005	514	1627	4000.3010 US1

APPLICANTS
Elliot Ehrich, Lincoln, MA;

**** CONTINUING DATA ***************************
This appln claims benefit of 60/564,542 04/22/2004 /KDC/

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
04/15/2005

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /KENDRA D CARTER/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		MA	4	~~25~~ 22	~~6~~ 4

ADDRESS

/KDC/

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886
UNITED STATES

TITLE

Naltrexone long acting formulations and methods of use

FILING FEE RECEIVED		
0.00	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

PTO-1449 REPRODUCED	ATTORNEY DOCKET NO.	APPLICATION NO.	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION	4000.3010 US1	11/083,167	
	APPLICANT		
	Elliot Ehrich		
August 17, 2005	FILING DATE	CONFIRMATION NO.	GROUP
(Use several sheets if necessary)	March 17, 2005	8002	1614

OIPE JC59
AUG 29 2005
PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS				
EXAMINER INITIAL	REF. NO.	DOCUMENT NUMBER	ISSUE DATE / PUBLICATION DATE	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	AA	4,882,335	11-21-1989	Sinclair
	AB	6,264,987	07-24-2001	Wright *et al.*
	AC	5,654,008	08-05-1997	Herbert *et al.*
	AD	5,792,477	08-11-1998	Rickey *et al.*
	AE	6,358,443	03-19-2002	Herbert *et al.*
	AF	6,306,425	10-23-2001	Tice *et al.*
	AG	5,407,609	04-18-1995	Tice *et al.*
	AH	4,719,219	01-12-1988	Arvidsson *et al.*
	AI	5,512,593	04-30-1996	Dante

U.S. COPENDING APPLICATIONS				
EXAMINER INITIAL	REF. NO.	APPLICATION SERIAL NUMBER	FILINGDATE	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT
	BA	60/554,658	03-19-2004	Elliott Ehrich, *et al.*
	BB	60/554,785	03-19-2004	Elliott Ehrich, *et al.*
	BC	11/082,420	03-17-2005	Elliott Ehrich, *et al.*
	BD	11/082,534	03-17-2005	Elliott Ehrich, *et al.*

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	MM-DD-YYYY PUBLICATION DATE	NAME OF PATENTEE OR APPLICANT OF CITED DOCUMENT	TRANSLATION YES	NO
	AL	WO 2004/108084 A2	12-16-2004	Alkermes Controlled Therapeutics, II		
	AM	WO 2004/064752 A2	08-05-2004	Alkermes Controlled Therapeutics, Inc.		

EXAMINER	DATE CONSIDERED

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C./

PTO-1449 REPRODUCED	ATTORNEY DOCKET NO.	APPLICATION NO.	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION	4000.3010 US1	11/083,167	
August 17, 2005 (Use several sheets if necessary)	APPLICANT: Elliot Ehrich		
	FILING DATE: March 17, 2005	CONFIRMATION NO.: 8002	GROUP: 1614

OIPE JC59 AUG 29 2005 PATENT & TRADEMARK OFFICE

		OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	AR	Swift, Robert M., "Drug Therapy for Alcohol Dependence," *New England J. of Med., 340*(19): 1482-1490 (1999).
	AS	Karam-Hage, Maher and Brower, Kirk J., "Gabapentin Treatment for Insomnia Associated With Alcohol Dependence," *Am. J. Psychiatry, 157*(1): 151-153 (2000).
	AT	Myrick, M.D., Hugh, *et al.*, "Gabapentin Treatment of Alcohol Withdrawal," *Am. J. of Psychiatry, 155*(11): 1626-1627 , (1998) .
	AU	Malcolm, M.D., Robert, *et al.*, "Update on Anticonvulsants for the Treatment of Alcohol Withdrawal," *Am. J. on Addictions, 10*(1): 16-23, Abstract Only, (2001) .
	AV	Swift, R., *et al.*, "Naltrexone Effects on Diazepam Intoxication and Pharmacokinetics in Humans," *Psychopharmacology, 135*(3): 256-262 (1998), Abstract Only.
	AW	Chaves, M.L., *et al.*, "Diazepam Inhibits Retroactive Interference of Memory in Humans: Pretreatment with Naltrexone Does Not Alter This Effect," *Braz. J. Med. Biol. Res., 23*(5): 417-421 (1990), Abstract Only.
	AX	Fidecka, S. and Langwinski, R., "Effects of Opioid Antagonists on Anticonvulsant and Hypnotic Activity of Benzodiazepines," *Pol. J. Pharmacol., 48*(4): 409-414 (1996), Abstract Only.
	AY	Longo, L.P., *et al.*, "Divalproex Sodium (Depakote) for Alcohol Withdrawal and Relapse Prevention," *J. Addict Dis., 21*(2): 55-64 (2002), Abstract Only.
	AZ	Minuk, G.Y., *et al.*, "The Use of Sodium Valproate in the Treatment of Alcoholism," *J. Addict Dis., 14*(2): 67-74 (1995), Abstract Only.
	AR2	Reoux, J.P., *et al.*, "Divalproex Sodium in Alcohol Withdrawal: A Randomized Double Blind Placebo-Controlled Clinical Trial," *Alcohol Clin. Exp. Res., 25*(9): 1324-1329 (2001), Abstract Only.

EXAMINER	/Kendra Carter/	DATE CONSIDERED	11/23/2010

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C./

Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1627

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Elliot Ehrich		
Application No.	11/083,167	Group No.	1627
Filed:	March 17, 2005	Examiner:	Kendra D. Carter
Confirmation No.	8002		

For: Naltrexone Long Acting Formulations and Methods of Use

AMENDMENT AFTER FINAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment is in response to the Final Office action mailed from the U.S. Patent and Trademark Office on July 20, 2010, in the above-identified application.

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **5** of this paper.

Please enter.

/KDC/

Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1627

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Elliot Ehrich		
Application No.	11/083,167	Group No.	1627
Filed:	March 17, 2005	Examiner:	Kendra D. Carter
Confirmation No.	8002		

For: Naltrexone Long Acting Formulations and Methods of Use

AMENDMENT AFTER FINAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment is in response to the Final Office action mailed from the U.S. Patent and Trademark Office on July 20, 2010, in the above-identified application.

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **5** of this paper.

Amendments to the Claims:

Please cancel Claims 21 and 22.

The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing:

1. (Currently Amended) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

2. (Previously Presented) The method of claim 1 comprising administering the long acting formulation in a dose comprising between about 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.

3. (Withdrawn/Original) A method of treating an individual in need of naltrexone comprising administering naltrexone, in the absence of co-administering alcohol, to an individual who has not undergone alcohol abstinence within three days, such as five days, prior to the naltrexone administration.

4. (Withdrawn/Original) The method of Claim 3 wherein the naltrexone is administered in a long acting formulation comprising naltrexone.

5. (Withdrawn/Original) A method of increasing the days prior to occurrence of alcohol consumption in an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration.

6. (Previously Presented) The method of claim 1 comprising administering the long acting formulation comprising naltrexone in a dosage between about 160 mg to about 480 mg naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five or more days before said administration.

7. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.

8. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.

9. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose of at least about 160 mg of naltrexone.

10. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 160 and 240 mg of naltrexone.

11. (Original) The method of claim 10 wherein the long acting formulation is administered in a dose of about 190 mg of naltrexone.

12. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 310 and 480 mg of naltrexone.

13. (Original) The method of Claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone.

14. (Original) The method of claim 1 wherein the long acting formulation is administered over a period of about 24 week period or longer.

15. (Previously Presented) The method of claim 1 further comprising a second administration of a long acting formulation comprising naltrexone at least about 7 days after the first administration.

16. (Original) The method of Claim 15 wherein the second long acting formulation is substantially similar to the first long acting formulation.

17. (Original) The method of Claim 15 wherein the second long acting formulation is the same as the first long acting formulation.

18. (Previously Presented) The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.

19. (Original) The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.

20. (Previously Presented) The method of claim 1 wherein naltrexone is administered by injection.

21-22. (Cancelled)

23. (Original) The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35 % by weight.

24-25. (Canceled)

26. (Currently Amended) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

REMARKS

Claims 21 and 22 are cancelled. Claims 1 and 26 are amended to incorporate the subject matter of allowable claim 22. Claims 1, 2, 6-20, 23 and 26 are under consideration. Claims 3-5 have been withdrawn. Claims 1-20, 23, and 26 are pending in the application. Reconsideration is respectfully requested.

Allowable Subject Matter

Applicants thank the Examiner for the indication of allowable subject matter with regard to claim 22. Applicants have amended claims 1 and 26 to incorporate the subject matter of claim 22. In view of the amendments to the claims, allowance of claims 1, 2, 6-20, 23 and 26 is respectfully requested.

Claim Rejections -35 U.S.C. §112

The Examiner has maintained the rejection of the claims 1, 2, 6-23 and 26 under 35 U.S.C. §112, first paragraph. In view of the amendments to claims 1 and 26 and all claims dependent thereon, it is believed that the rejection under this section is moot. Applicants respectfully request the withdrawal of the rejection.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

ELMORE PATENT LAW GROUP, P.C.

/Darlene A. Vanstone/

Darlene A. Vanstone
Registration No. 35,729
Tel: (978) 251 3509
Fax: (978) 251 3973
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: **October 20, 2010**

Electronic Acknowledgement Receipt

EFS ID:	8664357
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Hollie Wakefield
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	20-OCT-2010
Filing Date:	17-MAR-2005
Time Stamp:	15:28:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AAF.pdf	74803 233ebd3fe737ecae28282b23ab9eba84524247ff	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
	Total Files Size (in bytes):	74803	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/083,167	03/17/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/20/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 22	Minus	** 47	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/MOLIKI I. MAY/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

38421 7590 07/20/2010
ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
07/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/083,167	EHRICH, ELLIOT	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 26* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of May 5, 2010 made to the office action filed January 6, 2010. Claims 1-23 and 26 are pending. Claims 24 and 25 are cancelled and claims 3-5 are withdrawn. Claim 1 is amended.

The declaration filed October 5, 2009 has been considered and found persuasive. Particularly, the Applicant's application exhibits a serum AUC of naltrexone at least about three times or at least about two times greater than that achieved by 50 mg/day oral administration, whereas the formulation of Tice is similar to a 50 mg/day oral administration. In light of the declaration and/or the Applicant's arguments, the 35 U.S.C. 102(b) and 103(a) rejections are withdrawn.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 112, first paragraph rejection were found not persuasive, thus the rejection is upheld.

The Examiner still upholds that there is allowable subject matter, wherein claim 1 is amended to include the polymer of claim 22, but the Applicant's still do not agree because the limitation would deny Applicant's the full scope of their invention.

In light of the amended claim, the modified 35 U.S.C. 112, first paragraph rejection is below. The Applicant's arguments are also below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-23 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating an individual with a long acting formulation comprising naltrexone and polylactide-co-glycolide polymer wherein the serum AUC is at least about three times greater than that achieved by 50/mg/day oral administration, does not reasonably provide enablement for a formulation comprising any biocompatible polymer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that

achieved by 50 mg/day oral administration. The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration."

(2) The breadth of the claims:

Claims 1, 2, 6-23 and 26 embrace and read on a long acting naltrexone formulation with any biocompatible polymer. The specification does not enable any long acting naltrexone formulation comprising any biocompatible polymer that gives a serum

AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration.

(3) The state of the prior art:

The state of the art regarding any long acting naltrexone formulation comprising any biocompatible polymer providing a serum AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration is very low. Tice et al. teach muscular injectable naltrexone microsphere compositions and their use in reducing consumption of heroin and alcohol (see title and abstract). The composition comprises a matrix consisting of the polymer poly-(D,L-lactide) The naltrexone is released in a controlled manner for greater than 28 or about 32 days. Smaller doses may be administered after the first dose, because on continues to obtain release from the prior injected mirospheres to which is added the release from the lately administered microspheres, or one can enjoy enhanced levels of the naltrexone without increasing the amount of the microspheres which are administered (see abstract and column 6, lines 19-29). The microspheres are formulated from about 150-350 mg of naltrexone such that the plasma concentration is in a therapeutic range of at least about 2 ng/mL (see column 4, lines 36-38 and column 5, lines 60-63; addresses claims 1, 2, 6 and 9-13). The microsphere formulation gave an AUC of 1.19 times greater than that achieved by 50 mg/day oral administration (see column 14, lines 40-55). Naltrexone is employed in an amount in the range of 15 to 50 weight % (see claim 1).

(4) The predictability or unpredictability of the art:

The predictability of every long acting naltrexone formulation with any biocompatible polymer providing an AUC of naltrexone of at least about two or three times greater than that achieved by 50 mg/day oral administration is relatively low. In other words, just because there are potential of a long acting formulation of naltrexone comprising a biocompatible polymer to provide an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration, effective elevated AUC serum levels has yet to be completely established. As Tice et al. teaches, every long acting formulation with a biocompatible polymer and naltrexone does not give an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration. Therefore, because there is a "potential" or reaching the claimed AUC serum values, the actual long acting formulation that gives these results is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Tice et al.

(6) The amount of direction or guidance presented / working examples:

The specification as filed does not speak on or show any working examples any studies performed that any long acting formulation provides an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. In the instant case, the guidance of the specification as to a naltrexone and any biocompatible polymer long acting formulation providing an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration is completely lacking. Particularly, the specification teaches that the long acting formulation comprising DL PLGA (poly(lactide)-co-glycolide polymeric matrix (i.e. MEDISORB; see page 12, line 2; and page 15, line 1) in conjunction with psychosocial treatment is effective in treating heavy drinking (see page 24 in its entirety). In regards to its comparison to oral naltrexone, a definitive comparison of efficacy can not be made (see page 26, lines 5-10), but the Applicants attempted to compare the invention to other oral administration studies to show that the invention was effective in treating alcohol dependence with psychosocial therapy, than psychosocial therapy alone (see page 28 in its entirety and page 29, lines 1-5). There was no measurement of the claimed AUC measurements in comparison to the oral administration, just a comparison of treatment.

(7) The quantity of experimentation necessary:

The instant claims read on any long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. As discussed above the specification fails to provide any support for any long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every biocompatible polymer and combination of ingredients to comprise a formulation of naltrexone, or at least a subset with specific ingredients that is sufficiently representative of specific long acting naltrexone formulations, to determine if each formulation has a serum AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration. For example, to test for the claimed AUC, different formulation comprising different biocompatible polymers and other ingredients including naltrexone, would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration since parenteral administration can include several routs) would also have to be selected. Serum AUC measurements would have to be taken and then compared to the oral administration route. If desired serum AUC results did not result, the dosage regime and/or formulation would have to be varied, for example by changing the dosage amount or route of administration, until the desired serum AUC results were achieved.

If the desired serum AUC measurements were shown with a particular formulation, then another formulation would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each formulation to determine if the formulation has a serum AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration, in order to be able to fully carry out the invention. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for a long acting formulation comprising naltrexone and polylactide-co-glycolide polymer to provide an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration, but not for any biocompatible polymer.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

> Applicant's argue that Tice is not a reasonable example of unpredictability because Tice's objective was to show that naltrexone delivered intramuscularly was comparable to taking 50 mg oral tablets of naltrexone

> for one month. Thus, it can not be concluded that Tice failed to achieve a formulation of the present claims. Further, Example 3 provides a working example, and the Declaration of Ehrich filed Ocotber 5, 2009 provides further enablement. In regards to Examiner's statement of undue experimentation, any number of variables including AUC and testing the biocompatible polymer delivery systems are standard techniques that are provided in the art. Thus, it is well within the ability of the skilled person to adjust the various components of the polymer delivery systems such as excipients that alter erosion rates and time of release and systematically test several of these formulations to determine the effect on the desired feature.

The Examiner disagrees because Tice et al. provides evidence that not all biocompatible polymers provide an AUC of naltrexone at least about tree times greater than that achieved by 50 mg/day oral administration. As the Applicant's admits, there are numerous biocompatible polymers, not to mention those that have not been created yet. There is no predictability that every biocompatible polymer will give the same claimed effects, which is evidenced by Tice et al. Thus, there is unpredictability as well as undue experimentation. Although tests are known to acquire AUC measurements, one skilled in the art must test the biocompatible polymer, which could differ in structure and size, to see if when combined with naltrexone and administered parenterally provides the claimed effects. The Applicant's do not give a sub-genus of biocompatible polymers or even test this sub-genus to provide a sense of predictability such that undue experimentation would not be necessary. A search of the art did not produce a known group of biocompatible polymers that give a predictable AUC for drugs such as naltrexone. In regards to Example 3, the example simply demonstrates the effectiveness of treatment of the claimed formulation, but for the claimed composition to provide naltrexone at least about tree times greater than that achieved by 50 mg/day

oral administration. The Declaration further provides support of the claimed invention, but it is not commensurate in scope to the claim. It is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kendra D Carter/

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11083167
Filing Date	2005-03-17
First Named Inventor	Elliot Ehrich
Art Unit	1627
Examiner Name	Kendra D. Carter
Attorney Docket Number	4000.3010 US1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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/K.C./	1	01/015699	WO		2001-03-08	Southern Research Institute et al.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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/K.C./	1	Comer, Sandra D. et al., "Depot Naltrexone: Long-lasting Antagonism of the Effects of Heroin in Humans," Psychopharmacology, 159:351-360 (2002).	☐
/K.C./	2	Chiang, C.N. et al., "Kinetics of a Naltrexone Sustained-release Preparation," Clinical Pharmacology and Therapeutics, 36(5): 704-708.	☐

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11083167	EHRICH, ELLIOT
	Examiner	Art Unit
	KENDRA D CARTER	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/12/2009	04/29/2009	12/31/2009	07/06/2010					
	1	÷	✓	✓	✓					
	2	÷	✓	✓	✓					
	3	÷	N	N	N					
	4	÷	N	N	N					
	5	÷	N	N	N					
	6	÷	✓	✓	✓					
	7	÷	✓	✓	✓					
	8	÷	✓	✓	✓					
	9	÷	✓	✓	✓					
	10	÷	✓	✓	✓					
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	22	÷	✓	✓	✓					
	23	÷	✓	✓	✓					
	24	-	-	-	-					
	25	-	-	-	-					
	26			✓	✓					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
	KENDRA D CARTER	1617

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (eDAN)	4/29/09	KDC
EAST (search included)	4/29/09	KDC
Google (search terms similar to EAST search)	4/29/09	KDC
Search updated	12/9/09	KDC
Search updated	7/6/10	KDC

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	Art Unit	1627
	Examiner Name	Kendra D. Carter
	Attorney Docket Number	4000.3010 US1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Darlene A. Vanstone/	Date (YYYY-MM-DD)	2010-05-26
Name/Print	Darlene A. Vanstone	Registration Number	35,729

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(71) Applicant: SOUTHERN RESEARCH INSTITUTE [US/US]; 2000 Ninth Avenue South, P.O. Box 55305, Birmingham, AL 35255-5305 (US).

(72) Inventors: TICE, Thomas, R.; 1915 Forest River Court, Birmingham, AL 35244 (US). STAAS, Jay, K.; 101 Ashford Lane, Alabaster, AL 35007 (US). FERRELL, Teresa, M.; 608 Paden Drive, Vestavia Hills, AL 95226 (US). MARKLAND, Peter; 817 Tulip Poplar Drive, Birmingham, AL 95244 (US).

(74) Agents: ROWLAND, Bertram, I. et al.; Rae-Venter Law Group, P.C., P.O. Box 60039, Palo Alto, CA 94306-0039 (US).

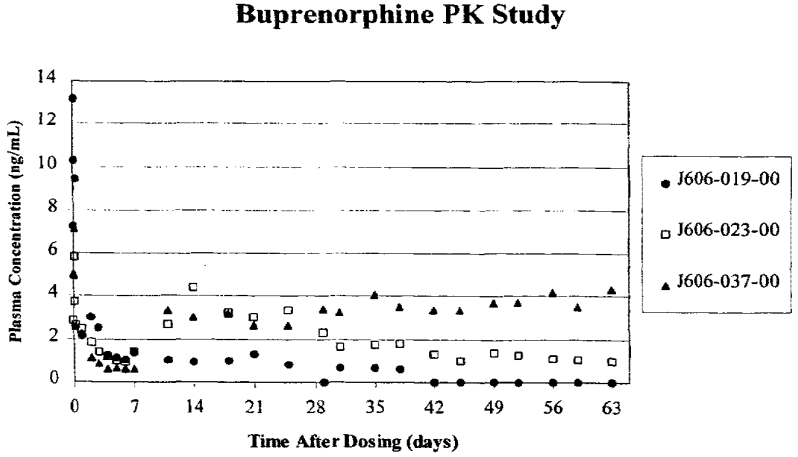
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(54) Title: INJECTABLE BUPRENORPHINE MICROPARTICLE COMPOSITIONS AND THEIR USE



(57) Abstract: An injectable slow-release partial opioid agonist or opioid antagonist formulation is provided comprising a partial opioid agonist or opioid antagonist in a poly(D,L-lactide) excipient with a small amount of residual ethyl acetate. Upon intramuscular injection of the composition, a partial opioid agonist or opioid antagonist is released in a controlled manner over an extended period of time. The composition finds use in the treatment of heroin addicts and alcoholics to reduce consumption of the abused substances. Of particular interest are the drugs buprenorphine, methadone and naltrexone.

WO 01/15699 A1

INJECTABLE BUPRENORPHINE MICROPARTICLE COMPOSITIONS AND THEIR USE

INTRODUCTION

Background

The disease of substance abuse remains a scourge on society. As it becomes more evident that there is a substantial genetic contribution to becoming addicted, helping addicted individuals to terminate their dependency or at least achieve a level of becoming a functional member of society, rather than treating substance abuse as a moral issue, has become increasingly accepted policy. Various programs have been put in place in the public and private sectors. In the private sectors, there are such organizations as Alcoholics Anonymous and Narcotics Anonymous, which play an important role in psycho-social support. In addition there are many private clinics which serve to provide both psycho-social support and medicinal support, using the somewhat limited repertoire of drugs which are available. In the public arena, there are the extensive programs to bring to the attention of young people and parents the hazards of substance abuse and discourage the young people from embarking on drug use. Also, there are the methadone programs, which are primarily public supported.

The number of substance abusing subjects in the United States is quite staggering. There are estimated to be about 15 million people who abuse alcohol, about 1.3 million who abuse cocaine in its many manifestations, about 0.8 million who abuse amphetamines and about 0.5 - 0.8 million who abuse heroin, in addition to the use of other drugs, such as the psychedelic drugs. Efforts to reduce the numbers of scheduled substances and alcohol users have been continuous and relatively unavailing. Those subjects who have entered programs have had a dismal record of relapse, so that only a small proportion of the people who do enter programs and are retained in the programs remain clean long after the completion of the program.

One significant factor in lack of retention and relapse is compliance. A repetitive act, such as taking a pill daily, is not a simple matter, even where the subject has no qualms about taking the pill. With the substance abuser, who may have physiological and emotional needs for the abused substance, the sustaining of the therapeutic routine is substantially more

difficult. Therapeutic techniques, which require perseverance on the part of the subject, decrease the likelihood of success of the treatment. It is therefore of great importance to be able to reduce the level of involvement of the subject where medicinal treatments are involved, particularly treatments which may involve frequent scheduling, monitoring of compliance, and sustaining a particular regimen.

In order to reduce the vicissitudes of compliance, there have been efforts to provide sustained-release methodologies. These have involved pumps, patches, depots and the like. Where the release implement is accessible to the subject, there is always the temptation to remove the implement during a craving episode. This opportunity, which may be an indication of will power, nevertheless, puts the subject at risk who succumbs to the temptation. By providing for a slow-release medicament which is introduced into the body, the temptation is avoided and the drug is released in accordance with a predetermined schedule over an arranged period of time. One can have implantable rods which are introduced surgically or microparticles which are injectable. Rods or microparticles can be devised to release the drug over an extended period of time in a controlled manner.

Microcapsules and microspheres are usually powders consisting of spherical particles 2 mm or less in diameter, usually 500 μm or less in diameter. If the particles are less than 1 μm, they are often referred to as nanocapsules or nanospheres. For the most part, the difference between microcapsules and nanocapsules or the difference between microspheres and nanospheres is their size.

A microcapsule or nanocapsule has its encapsulated material (hereinafter referred to as agent) centrally located within a unique membrane, usually a polymeric membrane. This membrane may be termed a wall-forming membrane, and is usually a polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release their agent at a constant rate (zero-order rate of release). Also, impermeable microcapsules can be used for rupture-release applications. A microsphere has its agent dispersed throughout the particle; that is, the internal structure is a matrix of the agent and excipient, usually a polymeric excipient. Usually, controlled-release microspheres release their agent at a declining rate (first-order). But microspheres can be designed to

release agents at a near zero-order rate. Microspheres tend to be more difficult to rupture as compared to microcapsules because their internal structure is stronger. Hereinafter, the term microparticles will include nanospheres, microspheres, microcapsules, nanocapsules, microbubbles (hollow particles), porous microbubbles, nanoparticles, microsponges (porous microspheres) and particles in general.

Various slow-release microparticles have been developed for a variety of drugs, but very few have been commercialized. There are many constraints on a satisfactory slow-release injectable formulation: the release of the drug must be over an extended period of time; during the time of treatment, the level of drug maintained in the subject must be an effective level, without reaching any hazardous level; the drug must be released slowly without a catastrophic dumping of the drug; the polymeric excipient used for the microparticles must be biodegradable and biocompatible; any residual chemicals must be below the maximum acceptable level; the microparticles must be small and capable of being administered by a syringe with a needle size which is acceptable to patients; the results must be reproducible, which requires that the process can be accurately controlled and is not unduly sensitive to minor changes in conditions; the injectable formulation must be sterile; and must have other characteristics which may be general or specific to the particular medicament. The properties of the microparticles are sensitive to many properties of the drug and excipient, as well as the selection of the process and the conditions under which the microparticles are prepared and subsequently processed.

Relevant Literature

Buprenorphine (N-cyclopropylmethyl-7-[1-(s)-hydroxy-1,2,2-trimethylpropyl]-6,14-endoethano-6,7,8,14-tetrahydronororipavine) is reported as effective in the treatment of opiate addiction using sublingual administration (U.S. Patent no. 4,935,428). Nasal administration of buprenorphine is reported in U.S. Patent no. 4,464,378. Long-acting drug antagonists are reported in U.S. Patent nos. 5,716,631 and 5,858,388. The use of buprenorphine for the treatment of drug dependence has been reported in numerous publications. Kuhlman et al., *Addiction* 1998 93:549-59; Schottenfeld et al., *Arch Gen. Psychiatry* 1997, 54:713-20; Strain et al., J. Clin. Psychopharmacol 1996, 16:58-67; are illustrative of a few of the reports. The combination of buprenorphine and naloxone is

reported in O'Connor et al., *Ann. Intern Med.* 1997, 127: 526-30.

Krantzler, et al., *Alcoholism:Clin and Exp Res* 1998, 22:1074-1079 report the treatment of alcoholics with a slow-release naltrexone particle injectable formulation. A number of studies were carried out by Reuning's laboratory concerning naltrexone and its use in a slow-release form: Reuning, et al., NIDA Re: Monograph Series, Jan. 1976, (4) p43-5; Reuning et al., *J. Pharmacokinet Biopharm*, Aug 1983, 11 (4), p369-87; Reuning, et al., *Drug Metab Dispos* Nov-Dec 1989, 17(6) p583-9; MacGregor et al., *J. Pharm Pharmacol*, Jan. 1983, 35(1) p38-42; Reuning et al., NIDA Res Monograph Series 1980, 28, p172-84. See also, Schwope et al., NIDA Res Monograph Series, 1975, (4), p13-8; Yolles et al., *J Pharm Sci* Feb 1975, 64(2) p348-9; Thies, NIDA Res Monograph Series, 1975 (4), p19-20; Schwope et al., NIDA Res Monograph Series, Jan 1976, 4, p13-18; Chiang et al., *Clin Pharmacol Ther* Nov. 1984 36(5) p704-8; Pitt et al., NIDA Res Monograph Series 1981, 28, p232-53; Chiang et al., Drug Alcohol Depend (SWITZERLAND), Sep 1985, 16 (1) p1-8; Yoburn et al., *J. Pharmacol Exp Ther*, Apr 1986, 237 (1) p126-130; Cha and Pitt, *J. Control Release*, 1989, 8(3), p259-265; Yamaguchi and Anderson, *J. Control Release*, 1992, 19(1-3), p299-314.

The use of naltrexone in the treatment of alcoholism is described in O'Malley et al., *Psychiatric Annals*, Nov 1995, 11, p681 - 688, as well as numerous other publications.

Patents of interest include U.S. Patent Nos. 4,568,559; 4,623,588; 4,897,267; and 5,486,362. U.S. Patent No.5,407,609 describes a process applicable to the process employed in the subject invention.

The use of polylactide in the preparation of drug-containing microparticles is described in Benita et al., *J Pharm Sci*, Dec 1984, 73(12) p1271-4; Speniehauer et al., ibid, Aug 1986, 75(8), p 750 -5; and Nihant et al., Oct 1994, 11(10), p1479-84.

SUMMARY OF THE INVENTION

Injectable, slow-release partial opiod agonist and opioid antagonist formulations are provided comprising a therapeutically effective amount of partial opioid agonist or opioid

antagonist (hereinafter referred to as drug or agent) released over an extended period of time and an excipient, for example, poly (D,L-lactide) polymer. The microparticles are under 125 μm in diameter and can be readily injected intramuscularly and provide at least about 0.5 ng/ml of drug over the extended period. Different release profiles are obtained depending upon the molecular weight of the polymer, the drug and the weight percentage of the drug. The microparticles are prepared by solvent extraction of a dispersed or dissolved drug polymer solution. Mixtures of microparticles of an agonist drug and an antagonist can be used to diminish any illicit use of the partial opiod agonist microparticles.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 compares the pharmacokinetic profiles for three different buprenorphine microparticle formulations after a single administration (25 mg/kg) in dogs.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Injectable slow-release partial opiod agonist and/or antagonist formulations are provided for use in the treatment of alcoholics and heroin addicts and such other indications for which partial opiod agonists or antagonists have been found to be efficacious. The partial opioid agonists or antagonists are characterized by having an effective plasma level in the range of about 0.5 – 1 ng/ml, usually 0.75 – 5 ng/ml, usually not more than about 3ng/ml. These partial opioid agonists include methadone, buprenorphine, and the like, while the antagonists include naltrexone.

Small sterilized microparticles are provided which can pass through a syringe needle and can be administered intramuscularly and remain at the site of injection for an extended period of time while continuously releasing a therapeutically effective amount of the drug for at least about 28 days. The release profile is found to be sensitive to the nature and amount of drug in the microparticles, the use of the free base as compared to the salt, and the inherent viscosity of the poly(D,L-lactide) excipient. The release profile appears to be less sensitive to the process conditions under which microparticles were prepared, the size distribution of the microparticles (as long as the composition substantially comprises microparticles in the range

of 20 to 125 μm) and the amount of solvent retained (so long as the amount of residual organic solvent is below 3 weight %).

The microparticles, as observed by scanning electron microscope (SEM), have the drug dispersed throughout the polymeric excipient. The microparticles have less than 3 weight % of ethyl acetate, the solvent used in the preparation of the microparticles. The weight percent of drug is from 10 to 70 weight %, usually 15 to 65 weight % and varies in range depending upon the inherent viscosity of the excipient. The inherent viscosity of the polymeric excipient is in the range of about 0.3 to 1.2 dL/g, as measured in chloroform at 30 °C and a concentration of 0.5 g/dL. Where the polymeric excipient has an inherent viscosity in the range of about 0.3 - 0.4 dL/g, the amount of drug will be in the range of about 10 to 50 weight %, usually 15 to 50 weight %, while when the inherent viscosity is in the range of about 1.0 - 1.2 dL/g, usually 1.0 - 1.1 dL/g, the amount of drug will be in the range of about 30 to 70 weight %, usually 35 to 65 weight %. For the most part, polymers having a viscosity in the range of 0.45 to 0.95 dL/g will not be employed, generally only low-molecular weight and higher-molecular weight polymers are used.

Mixtures of the polymers and microparticles made from such polymers or mixtures of such polymers may be used so as to deliver an effective amount of drug over the desired duration of treatment. Thus, the weight % of two different polymers may range from 1:99 to 99:1, more usually 10:90 to 90:10, where the lower-molecular-weight polymer will be in lesser amount than the higher-molecular-weight polymer. Similarly, low-drug-loaded, low-molecular-weight excipient microparticles (0.3 - 0.4 dL/g) may be mixed with higher drug loaded, higher molecular weight (1.0 - 1.2 dL/g) excipient microparticles in weight ratios of 5:95 to 95:5, where the lower-molecular-weight excipient microparticles will usually be present in from about 10 to 65 weight %.

Greater than about 90 weight % of the microparticles will have a diameter in the range of about 20 to 100 μm and less than 5 weight % will have a diameter less than about 10 μm.

To reduce agglomeration, the microparticles may be coated with an antiagglomerating agent, such as mannitol, which will be employed in less than about 50 weight %, usually less

than about 20 weight %, of the microparticles.

The microparticles are formulated in an appropriate vehicle to provide, depending upon the drug, from about 10 mg to 1 g, usually 50 to 750 mg of drug, for a single dose. For buprenorphine, the amount will generally be in the range of about 20 mg to 1 g, more usually from about 20 to 750 mg, while for methadone the amount will be from about 100 to 350 mg, more usually from about 150 to 250 mg, and for naltrexone will be in the range of about 150 to 300 mg. The vehicle may be sterile water, phosphate buffered saline, or other conventional vehicle for administering the microparticles. Additives may be present to improve suspendibility of the microparticles, slow the microparticles settling, and diminish discomfort from the injection. Conveniently, mannitol may be present in about 2 to 10 weight % of the vehicle, particularly 4 to 7 weight % of the vehicle. Other physiologically acceptable additives may include nonionic detergents, e.g. Tween, if present, will be present in from about 0.05 to 0.2 weight % of vehicle, viscosity enhancing agents, e.g. carboxymethylcellulose, in the range of about 0.1 to 1 weight % of vehicle, and other conventional additives, as appropriate. The amount of vehicle will generally be in the range of about 1 to 5 mL, usually 1 to 3.5 mL. The microparticles are dispersed in the vehicle immediately before use. Generally, the sterile microparticles will be stored in a sterile vial with a septum, where the microparticles may be mixed with the vehicle and then withdrawn into a syringe.

The microparticles are prepared by the process substantially as described in U.S. Patent No. 5,407,609. The process is an emulsion-based process which involves the preparation of an emulsion comprising an aqueous continuous phase (water and a surfactant and/or thickening agent) and a hydrophobic phase (polymer solvent, polymer and drug). After formation of the emulsion, the polymer solvent is extracted into an aqueous extraction phase. After a sufficient amount of polymer solvent is extracted to harden the microparticles, the microparticles are collected on sieves and washed to remove any surfactant remaining on the surface of the microparticles. The microparticles are then dried with a nitrogen stream for an extended period, e.g. about 12 hours, then dried in a vacuum oven at room temperature until at least substantially dry, conveniently for about 3 days.

A relatively simple apparatus may be employed for the preparation of microparticles. Using storage containers for the different streams, tubing, three-way valves and a homogenizer, the system is readily assembled. In addition, various monitoring devices may be included, such as flow meters, temperature monitors, particle size monitors, etc. The organic solution is introduced into a first tube connected to a three way valve, which connects to the aqueous continuous phase and to the homogenizer. By controlling the rate of flow of the two streams into the line connecting the homogenizer, the ratio of the two streams can be controlled, as well as the residence time in the homogenizer. The effluent from the homogenizer exits through a line which connects to a three-way valve through which the water stream is introduced. Again, the rate of flow ratio controls the amount of water to the homogenizer effluent stream. The residence time of the water extraction step is controlled by the length of tubing and the rate of flow of the combined streams. The microparticles are then segregated by size by passing through two or more sieves which eliminates microparticles outside the desired range.

For the preparation of the subject microparticles, the dispersed phase contains about 1-10 weight % of the drug and about 20-weight % polymer dispersed or dissolved (hereinafter both are included when referring to the polymer in a solvent as dispersed) in ethyl acetate. The continuous phase is an aqueous solution of about 1 - 10 weight % of poly(vinyl alcohol) and contains ethyl acetate at 1 to 7.5 weight %. The extraction phase is water. Generally, the amount of drug employed will be from about 10 to 50 weight % in excess of the final drug in the micromicroparticles. Temperatures may be ambient, generally being from about 15 to 30 °C.

After the microparticles have been collected and dried they may be stored at ambient temperatures, particularly in the range of about 0 – 20 °C in an oxygen and water free environment, or divided into aliquots into appropriate containers and sterilized. Various methods of sterilization may be employed, gamma irradiation being convenient.

The primary application for the subject formulations is as an intramuscular injectable, although subcutaneous injections may also be used. The subject will normally be a substance abuser, such as alcohol or heroin, but the subject compositions may be used for other

indications, such as obesity. The appropriate amount of the subject formulation is directly injected into a convenient site, e.g. gluteus. Thereafter, the subject may be monitored for drug plasma concentration to ensure that the amount is in the therapeutic range. When the drug plasma concentration falls below the therapeutic range, a subsequent injection may be made and this process repeated during the treatment period.

For heroin addicts, the subject will normally be detoxified by any one of a number of different ways, using buprenorphine, clonidine, naltrexone, etc. and checking with naloxone. A response to naloxone indicates that the subject has not been completely detoxified. Depending on the drug to be administered, usually a daily regimen of the drug dose will be made for at least about 3 days and not more than about 2 weeks, to ensure that the subject does not have an adverse reaction to the slow-release detoxification drug. Once it has been established that there is no adverse reaction, the depot form of the detoxification drug may then be administered.

By having microparticles which have long-term releasing capability, that is, greater than 14 days, usually greater than about 28 days, particularly greater than about 56 days, one can layer the administration, so that by giving injections in a periodic manner, one obtains an additive effect. In this manner, smaller doses may be administered after the first dose, since one continues to obtain release from the prior injected microparticles to which is added the release from the lately administered microparticles, or one can enjoy enhanced levels of the partial opioid agonist or opioid antagonist without increasing the amount of the microparticles which are administered. By providing for microparticles that can continue to release at levels in excess of 0.5 ng/ml, usually greater than about 1 ng/ml in blood, and depending on the prescribed plasma levels, usually not exceeding about 5 ng/ml, more usually not exceeding about 3g/ml, for greater than about 28 days after injection, preferably at least about 36 days, more preferably at least about 42 days, there can be a continuous plasma level, where the plasma level of the drug may be maintained in the therapeutic range. In this way, protection is greatly enhanced, as the subject is continuously exposed to a protective level of the drug and one can provide levels of the drug, which will inhibit response to a 50 mg challenge dose of heroin.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

General method of preparation of naltrexone microparticles

The following example is exemplary of the method of preparation generally, where the individual conditions are indicated in the following table. The chemical components are prepared as follows. Poly(D,L-lactide) is dissolved in ethyl acetate with stirring. The drug is added to the polymer solution and dissolved with stirring. Poly(vinyl alcohol) ("PVA") is dissolved in sterile water by slowly adding the PVA to the stirred water while heating the sterile water to a temperature of 90 °C. After complete dissolution of the PVA, the solution is allowed to cool and filtered through a 0.2 μm filter, which is followed by adding ethyl acetate to the PVA solution at 3 wt. %.

The system employed is substantially as described above, where for a batch of 15 g, using polymer having a viscosity of 1.07 dL/g and a theoretical drug concentration of 50% (relative to the combined weight of polymer and drug), the tubing employed is 0.5 inches i.d., and the length of the tubing for the final water extraction is 200 ft.

The equipment is set up as follows. The organic solution at a temperature of about 20 °C is pumped into the influent tubing at about 6 g/min. The PVA solution at about 20 °C is pumped into the influent tubing downstream from the organic solution at a rate of about 65 g/min. An emulsion is formed by continuously feeding this solution into a homogenizer. The effluent stream is diluted with sterile water at about 20 °C, which is pumped into the effluent stream at a rate of about 2000 g/min through tubing having sufficient length so as to provide an extraction time of about 6 minutes. The resulting microparticles are collected as particles which pass through a 125-μm sieve and are collected by a 20-μm sieve. The microparticles are continuously stirred and rinsed with sterile water to prevent premature drying. After ensuring that there are no more microparticles exiting the homogenizer, the homogenizer is stopped and the microparticles are rinsed with sterile water until there is no further PVA present.

After rinsing with sterile water the microparticles collected on the 20-mm sieve are dried under vacuum at room temperature for about 3 days. Dried product is obtained after a final sieving of the microparticles through a 125-μm sieve.

To reduce any agglomeration, the microparticles may be mixed with or thinly coated with mannitol. The microparticles may then be dispersed in an appropriate vehicle of sterile water comprising 0.5% carboxymethyl cellulose, 0.1% Tween 80 and 5.0% mannitol. The volume will be in the range of 1 - 3.5 mL to obtain satisfactory dispersion and release through an 18-gauge needle.

The following table indicates specific parameters for the preparation of the microparticles and the properties and performance of the microparticles *in vitro* and *in vivo*. In the *in vivo* study, dogs were injected intramuscularly with an 18-gauge needle with about 2 mL of solution containing the microparticles at the weight indicated in the table. The plasma was monitored for naltrexone at the times indicated. For the *in vitro* study, microparticles were maintained in 0.01M phosphate buffer, pH 7.4 at 37 °C and the residual naltrexone in the microparticles determined at the times indicated.

Table 1

Lot no.	Dog ID	Naltrexone loading, target wt%	Nalltrexone loading, actual wt%	Encapsulation efficiency, %	Temperature, °C	Polymer inherent viscosity, dL/g	Mean particle size, μm
92	2062-HM	50	38.3	77		1.07	57.76
	2067-HM						
	2073-IM						
142	2063-JM	50	42.5	85		1.07	44.36
	2066-JM						
	2070-KM						
118[a]	2065-FM	60	49.0	82	22	1.07	39.78
	2072-FM						
	2075-GM						
					[a] continuous phase was at room temperature (22 °C) and water saturated with 3% ethyl acetate		

a. remake of 74
b. batch prepared with dispersed drug
c. continuous phase was chilled to 11 °C and did not contain ethyl acetate
d. continuous phase was at room temperature (22 °C) and water saturated with 3% ethyl acetate
e. inherent viscosity measured in $CHCl_3$ at 30 °C at a concentration of 0.5 dL/g
f. Injection vehicle contained 2 wt. % sodium carboxymethyl cellulose and 1 wt. % Tween

Table 2

Lot no.	Naltrexone dose, mg	Microsphere dose	Vehicle, mL	Naltrexone in plasma, ng/ml) (hrs)					
				1 hr	2 hr	4 hr	8 hr	24 hr	48 hr
92	165	430.8	1.8	6.8	2.79	1.82	0.73	0.82	0.81
	147	383.8	1.8	6.33	4.14	2.34	0.64		0.86
	202.5	528.7	1.7	9.66	5.28	2.41	0.89	1.13	0.61
142	135	317.6	1.8	6.22	4.14	2.27	0.67	1.24	1.23
	165	388.2	1.8	5.19	3.5	2.33	0.68	0.72	1.04
	191.3	566.5	1.7	17.28	8.79	3.21	1.35	1.02	0.84
118	165	336.7	1.8	15.56	7.39		1.25	1.81	1.8
	133.5	272.4	1.9	7.6	4.04	1.77	0.79	0.71	0.9
	225	459.2	1.8	13.02	6.62	3.2	1.02	1.41	1.28

a. remake of 74
b. batch prepared with dispersed drug
c. continuous phase was chilled to 11 °C and did not contain ethyl acetate
d. continuous phase was at room temperature (22 °C) and water saturated with 3% ethyl acetate.
e. inherent viscosity measured in $CHCl_3$ at 30 °C at a concentration of 0.5 dL/g
f. Injection vehicle contained 2 wt. % sodium carboxymethyl cellulose and 1 wt. % Tween

Table 3

Lot no.	Naltrexone in plasma, ng/ml							
	3 day	7 day	11 day	14 day	18 day	21 day	29 day	35 day
92	1.17	24.95	5.14	3.99	3.27	3.63	1.38	0.7
	0.62	18.04	11.13	7.22	4.87	3.42	1.8	1.55
	1.29	40.1	17.71	7.74	4.43	4.2	1.26	NA
142	1.55	30.35	7.7	2.79	1.74	1.31	0.99	0.86
	1.03	23.3	5.82	2.38	2.1	2.15	1.46	0.87
	1.14	32.27	11.98	2.73	7.18	5.74	1.8	NA
118e	2.44	45.3	7.17	4.65	1.22	0.48	BQL	
	1.02	28.4	1.98	0.71	BQL			
	2.21	35.01	5.63	2.07	1.44	0.54	BQL	
BQL = Below quantitation level								

a. remake of 74
b. batch prepared with dispersed drug
c. continuous phase was chilled to 11 °C and did not contain ethyl acetate
d. continuous phase was at room temperature (22 °C) and water saturated with 3% ethyl acetate
e. inherent viscosity measured in $CHCl_3$ at 30 °C at a concentration of 0.5 dL/g
f. Injection vehicle contained 2 wt. % sodium carboxymethyl cellulose and 1 wt. % Tween

Lot 98 was above the quantitation level of 0.5ng/ml out to 140 days, while lots 82 and 142 were above the quantitation level up to 49 days.

Example 2

Preparation of Buprenorphine (free-base) Microparticles

A typical 10 g batch size was prepared as follows:

A 7% polymer solution was prepared by dissolving 5 g polymer in 66.2 g ethyl acetate. To this solution, 5 g of buprenorphine was added. This mixture (the dispersed phase, DP) was stirred until the drug dissolved.

A solution of 2 wt % poly(vinyl alcohol) was prepared in water. Sufficient ethyl acetate was added to this solution in order that the final concentration of ethyl acetate was 2.5 wt %. This solution (the continuous phase, CP) is called the CP phase.

The DP was pumped into a mixer at 27.2 g/min. Using separate tubing, the CP was pumped into the mixer as well at a flow rate of 124 g/min. The two solutions were kept separate until immediately before mixing took place inside the continuous-flow mixer head. Mixing was performed at a stir speed of 870 rpm. The emulsion coming out of the mixer was extracted using

water that was pumped at a rate of 2050 g/min to form a microparticle suspension. The suspension was collected, by hand, across 125-μm and 25-μm sieves. The portion of microparticles collected on the 25-μm screen was added to a tank of fresh water and stirred for 3 hours under ambient conditions. The microparticles were again collected by sieving and the portion obtained on the 25-μm screen was removed and dried by lyophilization. The final dried powder passed through a 125-μm sieve and was characterized with respect to drug content and particle size distribution (See Table 4).

Example 3

Preparation of Buprenorphine (free-base) Microparticles

A typical 20 g batch size was prepared as follows:

A 4.1% polymer solution was prepared by dissolving 6.3 g polymer in 146.6 g ethyl acetate. To this solution, 11.6 g of buprenorphine was added. This mixture (the dispersed phase, DP) was stirred until the drug dissolved.

A solution of 1 wt % poly(vinyl alcohol) was prepared in water. Sufficient ethyl acetate was added to this solution in order that the final concentration of ethyl acetate was 2.5 wt %. This solution (the continuous phase, CP) is called the CP phase.

The DP was pumped into a mixer at 25.9 g/min. Using separate tubing, the CP was pumped into the mixer as well at a flow rate of 127.2 g/min. The two solutions were kept separate until immediately before mixing took place inside the continuous-flow mixer head. Mixing was performed at a stir speed of 726 rpm. The emulsion coming out of the mixer was extracted using water that was pumped at a rate of 2038 g/min to form a microparticle suspension. The suspension was collected, by hand, across 125-μm and 25-μm sieves. The portion of microparticles collected on the 25-μm screen was added to a tank of fresh water and stirred for 3 hours under ambient conditions. The microparticles were again collected by sieving and the portion obtained on the 25-μm screen was removed and dried by lyophilization. The final dried powder passed through a 125-μm sieve and was characterized with respect to drug content and particle size distribution (See Table 4).

Table 4.

Characterization of Buprenorphine Microspheres

Lot Number	Poly(DL-lactide) IV, dL/g[a]	Drug content, wt % buprenorphine	Mean particle size, μm
J606-019-00	0.37	21.2	52.8
J606-023-00	0.37	43.1	57.2
J606-037-00	1.07	44.1	63.1
J606-103-00	1.07	60.9	64.9

[a] IV = inherent viscosity (chloroform, 0.5 g/dL, 30 °C)

Pharmacokinetics of a single administration in dogs (25 mg buprenorphine/kg) was measured using microparticles that received about 2.5 Mrad gamma-irradiation.

Table 5.

Pharmacokinetic Data in Dogs

Time	Buprenorphine plasma conc, ng/mL		
	J606-019-00	J606-023-00	J606-037-00
1 hr	7.23	2.86	4.98
2 hr	10.3	5.80	7.13
4 hr	13.2	3.75	4.92
8 hr	9.42	2.62	2.58
24 hr	2.22	2.45	2.27
48 hr	3.01	1.85	1.15
72 hr	2.54	1.42	0.86
Day 5	1.26	1.22	0.6
Day 6	1.16	0.98	0.66
Day 7	1.03	0.94	0.6
Day 8	1.39	1.45	0.59
Day 12	1.05	2.71	3.37
Day 15	0.96	4.41	3.02
Day 19	1.00	3.25	3.21
Day 22	1.30	3.01	2.64
Day 26	0.81	3.33	2.62
Day 30	BQL[a]	2.33	3.40
Day 32	0.66	1.63	3.25
Day 36	0.68	1.75	4.04
Day 39	0.58	1.82	3.53
Day 43	BQL	1.30	3.34
Day 46	BQL	1.00	3.35
Day 50	BQL	1.36	3.66
Day 53	BQL	1.26	3.74
Day 57	BQL	1.12	4.18
Day 60	BQL	1.03	3.53
Day 64	BQL	0.98	4.32

[a] BQL = below quantitation limit of 0.5 ng/mL

It is evident from the above results that a long term supply of a partial opiod agonist or

opioid antagonist at a physiologically effective concentration can be provided in vivo. In this way, compliance problems associated with the requirement of taking a pill daily can be avoided. Monitoring to determine whether the subject has taken the daily pill is obviated. The subject is better able to deal with the problem of substance abuse, being aware that the subject has better control in the case of alcoholism and will not obtain the desired euphoria from heroin. Counseling can be more effectively performed, since the subject will be discouraged from taking heroin and in the case of alcoholism, will be better able to cope with fewer drinks. In this way, subjects will be able to function and fulfill their obligations to their families and society.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A microparticle composition comprising a buprenorphine free base in an amount in the range of 10 to 70 weight %, poly(D,L-lactide) as a excipient, and less than about 3 weight % ethyl acetate, capable of providing a physiologically effective level of to reduce the consumption of heroin and/or alcohol when administered intramuscularly in a mammal over a period of about 28 days, at least 90 weight % of said microparticle composition comprising microparticles having a diameter in the range of 20 to 125 μm.

2. A microparticle composition according to Claim 1, wherein said buprenorphine is present in an amount in the range of 15 to 50 weight %, said poly(D,L-lactide) has an inherent viscosity in the range of about 0.3 to 0.4 dL/g and said ethyl acetate is present in from about 0.1 to 3 weight %.

3. A microparticle composition according to Claim 1, wherein said buprenorphine is present in an amount in the range of 30 to 65 weight %, said poly(D,L-lactide) has an inherent viscosity in the range of about 1.0 to 1.1 dL/g and said ethyl acetate is present in from about 0.1 to 3 weight %.

4. A microparticle composition according to Claim 1, wherein said poly(D,L-lactide) is a mixture of poly(D,L-lactide)s of differing inherent viscosity.

5. A microparticle composition according to Claim 1, wherein said composition is a mixture of microparticles which differ in at least one of weight % of buprenorphine or poly(D,L-lactide)s of differing inherent viscosity.

6. A microparticle composition according to Claim 1, wherein said microparticles are prepared by introducing a solution of said buprenorphine and poly(D,L-lactide) in ethyl acetate into an aqueous ethyl acetate containing solution of poly(vinyl alcohol) to form an emulsion and adding said emulsion to water to extract ethyl acetate to form microparticles, and isolating the resulting microparticles.

7. A formulation for injection comprising a microparticle composition according to Claim 1, carboxymethyl cellulose, Tween and mannitol.

8. A method for reducing the consumption of heroin and/or alcohol by a subject abusing at least one of heroin and alcohol, said method comprising:

administering intramuscularly an effective dose of a microparticle composition according to Claim 1 in an amount to inhibit the consumption of heroin and alcohol, whereby the consumption of heroin and/or alcohol is reduced.

9. A method for reducing the consumption of heroin and alcohol by a subject abusing at least one of heroin and alcohol, said method comprising:

administering an effective dose of a microparticle composition according to Claim 1, which composition continues to release said buprenorphine for a period greater than 28 days at at least an effective dose;

prior to the level of said buprenorphine falling below an effective dose, administering a second dose of said microparticle composition, whereby the combination of said original effective dose and said second dose provide an effective dose of said buprenorphine for a second period of at least an additional 28 days; and

repeating said adminstration to have said buprenorphine being released from both a prior adminstration of said microparticle composition and the lately administered microparticle composition to maintain said effective dose of said buprenorphine.

10. The method according to Claim 9, wherein at least one of said period and said second period is about 60 days.

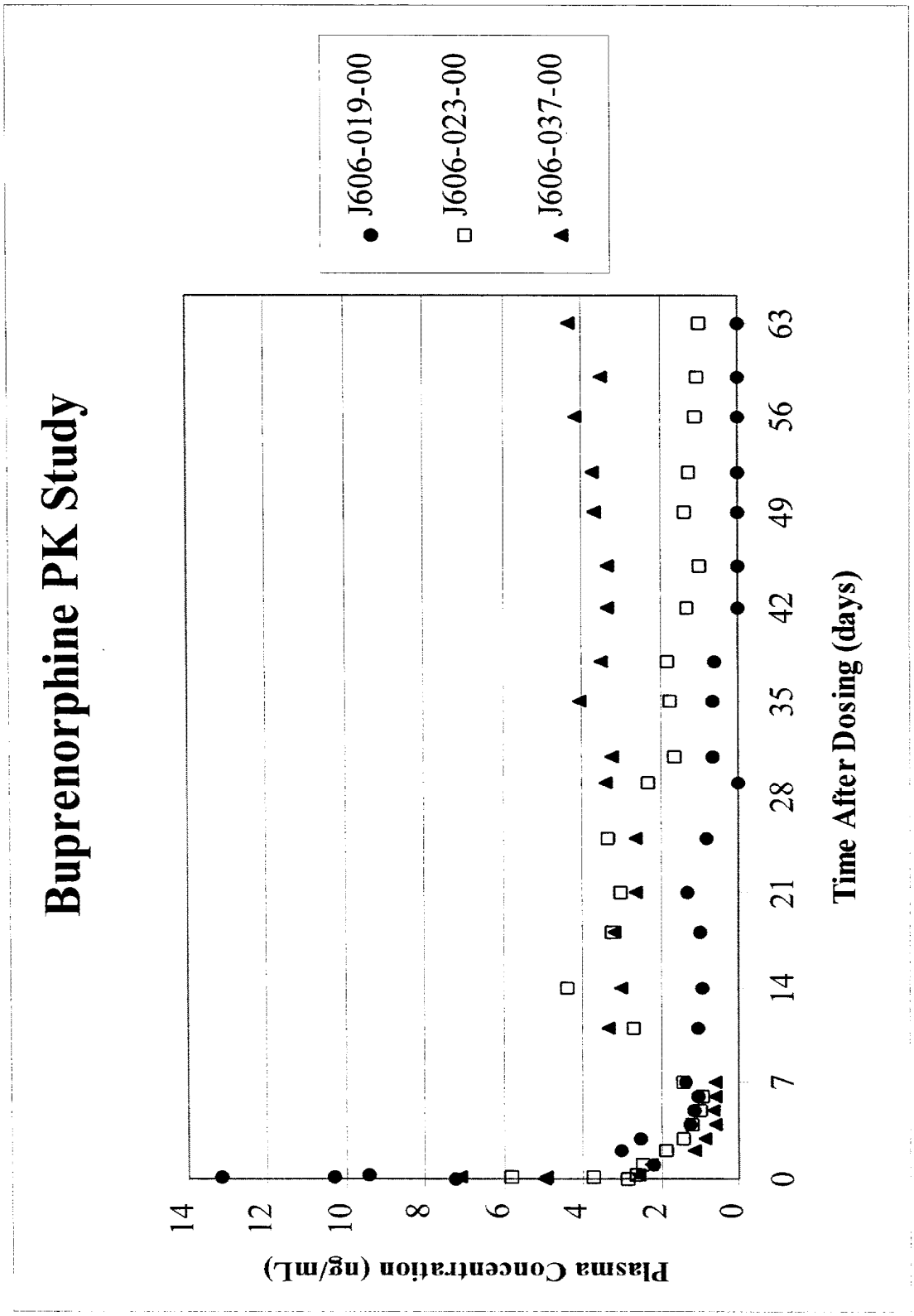

Buprenorphine PK Study
J606-019-00
J606-023-00
J606-037-00
Plasma Concentration (ng/mL)
0
2
4
6
8
10
12
14
Time After Dosing (days)
0
7
14
21
28
35
42
49
56
63

Figure 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/23390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/485 A61K9/50 A61P25/32 A61P25/36 A61K9/16

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)
IPC 7 A61K

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 practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 631 781 A (EUROCELTIQUE) 4 January 1995 (1995-01-04) claims page 8, line 28 - line 42 ---	1-10
A	EP 0 144 243 A (RECKITT & COLMAN) 12 June 1985 (1985-06-12) claims examples 4-7 page 8, line 20 -page 25 ---	1-10
A	WO 90 03783 A (E.I. DU PONT DE NEMOURS AND COMPANY) 19 April 1990 (1990-04-19) claims 1,7,8,10 page 18, line 9 - line 15 examples 19,20 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 but 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	Date of mailing of the international search report
18 January 2001	26/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/23390

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 537 559 A (ATRIX) 21 April 1993 (1993-04-21) claims 1,5,9,10,14,15,18 examples 1,3,4 -----	1-10

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

International Application No
PCT/US 00/23390

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

....ormation on patent family members

Internr ·nal Application No
PCT/uS 00/23390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Electronic Acknowledgement Receipt

EFS ID:	7693687
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Hollie Wakefield
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	26-MAY-2010
Filing Date:	17-MAR-2005
Time Stamp:	16:28:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		SIDS.pdf	30836 d12ee3c73a32b8ef5a4e2dd3e970628b9e7ccc45	yes	3

	Multipart Description/PDF files in .zip description				
	Document Description	Start	End		
	Information Disclosure Statement (IDS) Filed (SB/08)	1	2		
	Transmittal Letter	3	3		
Warnings:					
Information:					
2	Foreign Reference	WO0115699A1.pdf	1064610 1c5e6d8cc7bbbcf58dd63f8d0843f906970e487a	no	24
Warnings:					
Information:					
3	NPL Documents	Chiang.pdf	366086 4e8f11ab0cf757773f0c699234912053ad2ee7c8	no	6
Warnings:					
Information:					
4	NPL Documents	Comer.pdf	882185 957aa276908eb2fb656b6999c9c59ed9056d9db2	no	10
Warnings:					
Information:					
		Total Files Size (in bytes):	2343717		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Elliot Ehrich		
Application No.	11/083,167	Group No.	1627
Filed:	March 17, 2005	Examiner:	Kendra D. Carter
Confirmation No.	8002		

For: Naltrexone Long Acting Formulations and Methods for Use

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment is in response to the Office action mailed from the U.S. Patent and Trademark Office on January 6, 2010, in the above-identified application.

A Petition for Extension of Time for one month and the appropriate fees are being filed concurrently.

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **5** of this paper.

Amendments to the Claims:

The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing:

1. (Currently Amended) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration.

2. (Previously Presented) The method of claim 1 comprising administering the long acting formulation in a dose comprising between about 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.

3. (Withdrawn/Original) A method of treating an individual in need of naltrexone comprising administering naltrexone, in the absence of co-administering alcohol, to an individual who has not undergone alcohol abstinence within three days, such as five days, prior to the naltrexone administration.

4. (Withdrawn/Original) The method of Claim 3 wherein the naltrexone is administered in a long acting formulation comprising naltrexone.

5. (Withdrawn/Original) A method of increasing the days prior to occurrence of alcohol consumption in an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration.

6. (Previously Presented) The method of claim 1 comprising administering [[a]] the long acting formulation comprising naltrexone in a dosage between about 160 mg to about 480 mg naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five or more days before said administration.

7. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.

8. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.

9. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose of at least about 160 mg of naltrexone.

10. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 160 and 240 mg of naltrexone.

11. (Original) The method of claim 10 wherein the long acting formulation is administered in a dose of about 190 mg of naltrexone.

12. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 310 and 480 mg of naltrexone.

13. (Original) The method of Claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone.

14. (Original) The method of claim 1 wherein the long acting formulation is administered over a period of about 24 week period or longer.

15. (Previously Presented) The method of claim 1 further comprising a second administration of a long acting formulation comprising naltrexone at least about 7 days after the first administration.

16. (Original) The method of Claim 15 wherein the second long acting formulation is substantially similar to the first long acting formulation.

17. (Original) The method of Claim 15 wherein the second long acting formulation is the same as the first long acting formulation.

18. (Previously Presented) The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.

19. (Original) The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.

20. (Previously Presented) The method of claim 1 wherein naltrexone is administered by injection.

21. (Original) The method of claim 1 wherein the long acting formulation comprises a polylactide polymer or a poly lactic acid polymer.

22. (Previously Presented) The method of claim 1 wherein the long acting formulation comprises a polylactide-co-glycolide polymer.

23. (Original) The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35 % by weight.

24-25. (Canceled)

26. (Previously Presented) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration.

REMARKS

Claim 1 has been amended. Support for the amendment to claim 1 is found on page 4, lines 19-21 and page 7, line 4. The term "biocompatible polymer" is also defined in column 6, line 65 to column 7, line 58, of U.S. Pat. No. 6,358,443, incorporated by reference on page 5, line 6 of the present application. Claims 3-5 have been withdrawn. Claims 1-23 and 26 are pending in the application. Reconsideration is respectfully requested.

Claim Rejections 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1, 2, 6-23 and 26 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the instant claims are drawn to a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. The Examiner asserts that the specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation citing the *Wands* factors (*In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988). Applicants respectfully disagree.

The Examiner argues that the predictability of every long acting formulation providing an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration is relatively low. The Examiner makes reference to Tice (U.S. Pat. No. 6,306,425) as the state of the art and the Examiner asserts that Tice teaches that every long acting formulation of naltrexone does not give an AUC of naltrexone of at least about two or three times greater than that achieved by 50 mg/day oral administration. The Examiner concludes that because there is a "potential" of reaching the claimed AUC serum values, the actual long acting formulation that gives these results is unpredictable.

The Examiner further argues that the specification provides no working examples. The Examiner also asserts that Applicants have failed to provide any

information sufficient to practice the claimed invention, absent undue experimentation.

With regard to the Examiner's position on unpredictability, the Examiner uses the previously cited Tice patent as evidence that not *every* long acting formulation results in the presently claimed AUC and the actual long acting formulation that gives these results is unpredictable. However, Tice is not a reasonable example of unpredictability. Tice did not *attempt* to achieve a naltrexone formulation that provided an AUC that was at least 2 times greater than the AUC for oral naltrexone (50 mg). Tice's objective was to show that naltrexone delivered intramuscularly was *comparable* to taking 50 mg oral tablets of naltrexone for one month (column 14, lines 59-64). Applicants were the first to discover that higher AUC could be achieved with an extended release formulation.

Thus, it can not be concluded that Tice *failed* to achieve a formulation having the presently claimed AUC. Tice did not have the benefit of the presently claimed invention which teaches that such AUC are possible. Applicants will establish, once it is understood that the presently claimed AUC can be achieved, it is well within the skill in the art to test any number of long acting formulations without undue experimentation to determine which formulations provide the claimed AUC.

It is also well established that the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (MPEP 2164.08(b)). Thus the Examiner's assertion that *every* long acting formulation must predictably provide the claimed AUC is not the standard. In order to expedite prosecution of the present application, Applicants have amended claim 1 to recite long-acting formulations that comprise biocompatible polymers. As Applicants will show herein those formulations falling within the present claims are determined using

standard means without undue experimentation.

With regard to the Examiner's statement that the application does not include a working example, Applicant respectfully disagrees. There are five working examples in the present specification. While Example 3 is not the head to head comparison, it is a comparison of actual *in vivo* data collected by Applicants on the one hand and peer reviewed data and analysis on the other hand. Such a semi quantitative comparison is a scientifically sound comparison generally acceptable in research and is indeed a working example.

Using the materials and methods set forth in the Examples of the present specification, a head to head comparison between oral naltrexone (50 mg) and a long acting naltrexone formulation of the invention (i.e. MEDISORB® Naltrexone 380 mg and 190 mg) was carried out and the data resulting from those studies indicated that the claimed AUC was achieved. See the § 132 Declaration of Dr. Elliot Ehrich submitted with the Response dated October 5, 2009. Note that Table 8 of Exhibit A of the Ehrich Declaration shows that the 380 mg dose has an AUC that is at least 3.3 times greater than the AUC of the per day dose of oral regimen of 50 mg per day naltrexone. Based on the proportionality observed between the 190 and 380 mg doses of MEDISORB® naltrexone, the 190 mg was reasonably predicted to be about 2 fold higher than the AUC following oral dosing of 50 mg per day for 28 days (page 2 of the Ehrich Declaration). In accordance with MPEP 2164.05 an enablement rejection can be overcome by a declaration after the filing date that demonstrates that the claimed invention works using the patent application as a guide.

With regard to the Examiner's statement that undue experimentation is required, Applicants respectfully disagree. Numerous long acting biocompatible formulations are known in the art. Several of these are mentioned on page 5, lines 2-12 of the present application and include the MEDISORB® biocompatible polymer delivery system exemplified in the Examples and discussed in the Ehrich declaration. The chemistry around these various biocompatible polymer delivery systems is well established. Any number of variables including AUC is easily

tested using standard techniques in this highly studied art.

The art discussed on page 5, lines 2-12 of the present application confirms this. For example, U.S. Patent 6,264,987 (Exhibit A) cited on page 5, line 5 of the present application discloses in Example 6, experiments correlating the effect of temperature on the relationship between molecular weight of the long acting biocompatible polymer formulation and the erosion rate of the polymer under physiological conditions (column 10, lines 18-64). Figure 3 of U.S. Patent 6,264,987 (Exhibit A) depicts a graph of molecular weight as a function of solution hold time at varying temperatures. The graph of FIG. 3 provides data from which the skilled person can establish an algorithm for calculating sustained release as a function of one or more variables of the particles. Obtaining this information required standard procedures for establishing release of the active by the polymer under physiological conditions.

Tice et al. cited by the Examiner (U.S. 6,306,425) discloses *in vivo* experiments testing six different formulations of naltrexone long acting polymer formulations to determine the response in humans to different protocols for administration and the naltrexone release profile of a number of the six formulations (column 13, beginning on line 1). From this data, Tice was able to generally conclude that a long term supply of naltrexone at a physiologically effective concentration can be provided *in vivo*. Once again these tests are well within the skill in the art.

Other evidence that shows the standard nature of testing of biocompatible polymer delivery systems includes, but is not limited to the following. All patents and applications referred to in the following section are provided herewith as exhibits attached to this response.

In 1997, Cha *et al.* US 5,702,717 (Exhibit B), describes an injectable block copolymer drug delivery system. The copolymer is made up of a hydrophobic block (A) selected from the group consisting of poly (a-hydroxy acids) and poly (ethylene carbonate), and a hydrophobic block (B) comprising polyethylene glycol. These formulations were studied using standardized tests for the controlled release of human calcitonin, platelet-derived

growth factor (PDGF-B), and insulin (Example 8). U.S. Patent No. 6,004,573 (Exhibit C) describes the use of water soluble ABA or BAB type triblock polymers for drug delivery. The polymer is made up of a major amount of a hydrophobic polymer (PLGA or PLA) as the A block and a minor amount of a hydrophilic PEG block. Using standard testing, the release rate of the drug may be altered by changing various parameters such as adjusting hydrophobic/hydrophilic content, molecular weight, polymer concentration, and polydispersity of the triblock copolymer (Examples 3, 4, and 5).

U.S. Publication No. 2002/0015737 (Exhibit D), discloses proteins deposited onto sparingly soluble biocompatible particles for controlled protein release into a biological environment from a polymer matrix. Example 8 discloses *in vivo* pharmacokinetic studies of hGH sustained release formulations in rats. These standard studies were conducted in rats to verify the effect of hGH deposited on sparingly water soluble zinc carbonate salt. Sprague-Dawley rats were given one of five different formulations having various solution bases.

Multiblock biodegradable macromers including at least four polymeric blocks are described U.S. Publication No. 2002/0151650 (Exhibit E). This application discloses that at least two polymeric blocks are hydrophobic and at least one is hydrophilic, and the macromer should include a crosslinkable group. The block copolymers may be linear, star-shaped, or branched. The macromers include one or more regions that have thermo-responsive properties such as poloxamers. Using standard *in vitro* testing, the composition of the macromers can be altered to produce hydrogels with desired drug delivery properties. Macromers were synthesized with a wide range of hydrophobicity and tested for drug release properties using standard techniques (see, Examples 11-13). It was shown that the certain formulations possessed a significant ability to retard water permeation and drug release.

Thus, it is well within the ability of the skilled person to, for example, adjust the various components of the polymer delivery systems such as excipients that alter erosion rates and time of release and systematically test several of these formulations to determine the effect on the desired feature. An algorithm for

calculation of each of the components can then be developed for each class of biocompatible polymer and used to screen one or more types of compatible biopolymers using standard techniques to determine which are capable of meeting the AUC.

In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known," 858 F.2d at 740, 8 USPQ2d at 1406. In accordance with MPEP 2164.01, it is well established that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Given that the Examiner agrees that the level of skill in the art is high, and Applicants has shown that the methods needed to practice the invention are disclosed in the application *and* are well known with regard to testing a variety of long acting formulations comprising biocompatible polymers, it is clear that undue experimentation is not required.

With regard the Examiner's assertion that the amount of testing would be "exhaustive", according to MPEP 2164.06, the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient

direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)." 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

In view of the above discussion, Applicants submit that the present claims are fully enabled. Withdrawal of the rejection under this section is respectfully requested.

Allowable Subject Matter

Applicants thank the Examiner for the telephone call and the indication of allowable subject matter upon amendment of claim 1 to include the subject matter of claim 22. However, in view of the above discussion the Examiner can see that limiting Applicants to a single polymer would deny Applicants the full scope of their invention. Given the present application as a guide, highly skilled practitioners in this art can rapidly screen, using standard techniques, any number of long acting formulations comprising a variety of biocompatible polymers to determine which of those formulations meets the presently claimed AUC. In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Therefore, Applicants respectfully request reconsideration of amended claim 1 and all claims dependent thereon.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

ELMORE PATENT LAW GROUP, P.C.

/Darlene A. Vanstone/

Darlene A. Vanstone
Registration No. 35,729
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: **April 5, 2010**

PTO/SB/22 (07-09)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*)	Docket Number (Optional) 4000.3010 US1
Application Number 11/083,167	Filed March 17, 2005
For Naltrexone Long Acting Formulations and Methods for Use	
Art Unit 1627	Examiner Kendra D. Carter

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$130	$65	$ 130
☐	Two months (37 CFR 1.17(a)(2))	$490	$245	$
☐	Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐	Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐	Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 502807.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 35729

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Darlene A. Vanstone/ — Signature

May 5, 2010 — Date

Darlene A. Vanstone — Typed or printed name

(978) 251-3509 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

US006264987B1

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

(10) **Patent No.: US 6,264,987 B1**
(45) **Date of Patent: Jul. 24, 2001**

(54) **METHOD FOR PREPARING MICROPARTICLES HAVING A SELECTED POLYMER MOLECULAR WEIGHT**

(75) Inventors: **Steven G. Wright**, Madeira; **Michael E. Rickey**, Loveland; **J. Michael Ramstack**, Lebanon; **Shawn L. Lyons**; **Joyce M. Hotz**, both of Cincinnati, all of OH (US)

(73) Assignee: **Alkermes Controlled Therapeutics Inc. II**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/575,075**

(22) Filed: **May 19, 2000**

(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/50; B01J 13/02

(52) **U.S. Cl.** **424/489**; 424/497; 424/484; 264/41; 264/46; 427/213.3; 427/213.36

(58) **Field of Search** 424/489, 497; 264/41, 46; 427/213.3, 213.36

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,654,008 * 8/1997 Herbert et al. 424/489

* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Blessing Fubara
(74) *Attorney, Agent, or Firm*—Andrea G. Reister; Covington & Burling

(57) **ABSTRACT**

A method for preparing microparticles having a selected polymer molecular weight. The hold time and temperature of a solution containing a nucleophilic compound and a polymer having a starting molecular weight are controlled in order to control the molecular weight of the polymer in the finished microparticle product. In this manner, a selected polymer molecular weight in the finished microparticle product can be achieved from a variety of starting material molecular weights.

50 Claims, 4 Drawing Sheets

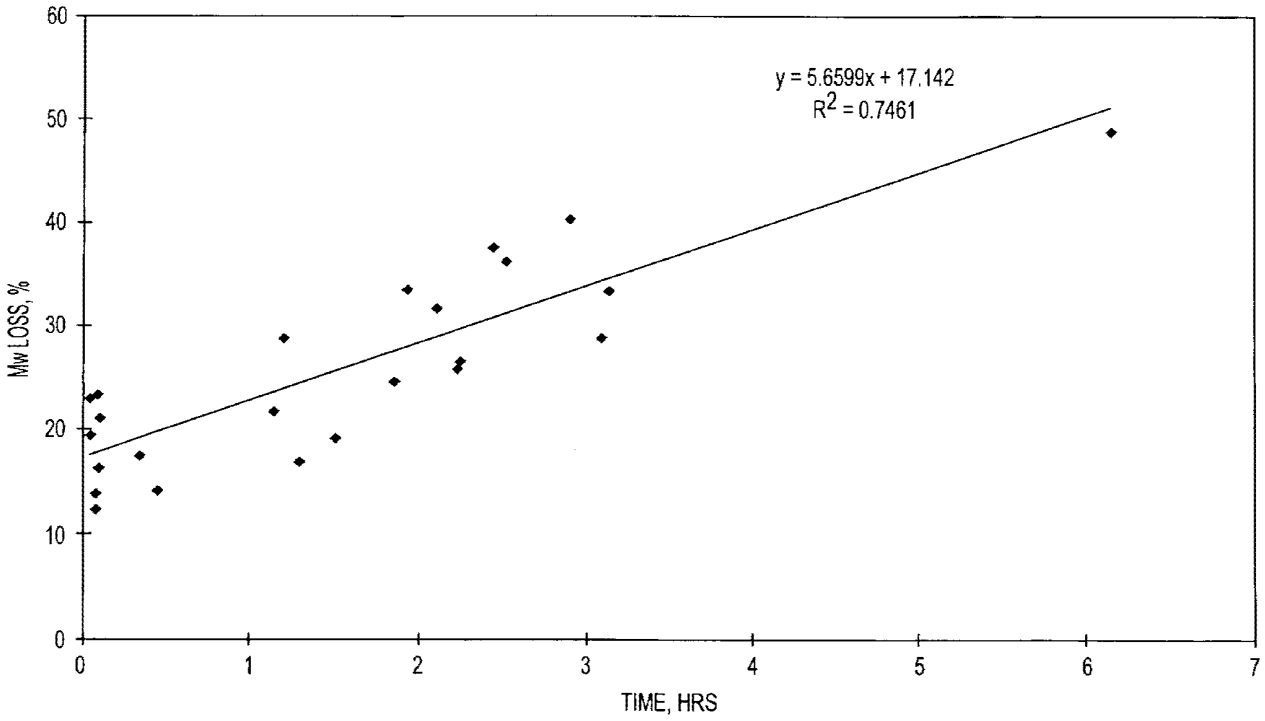


EXHIBIT A

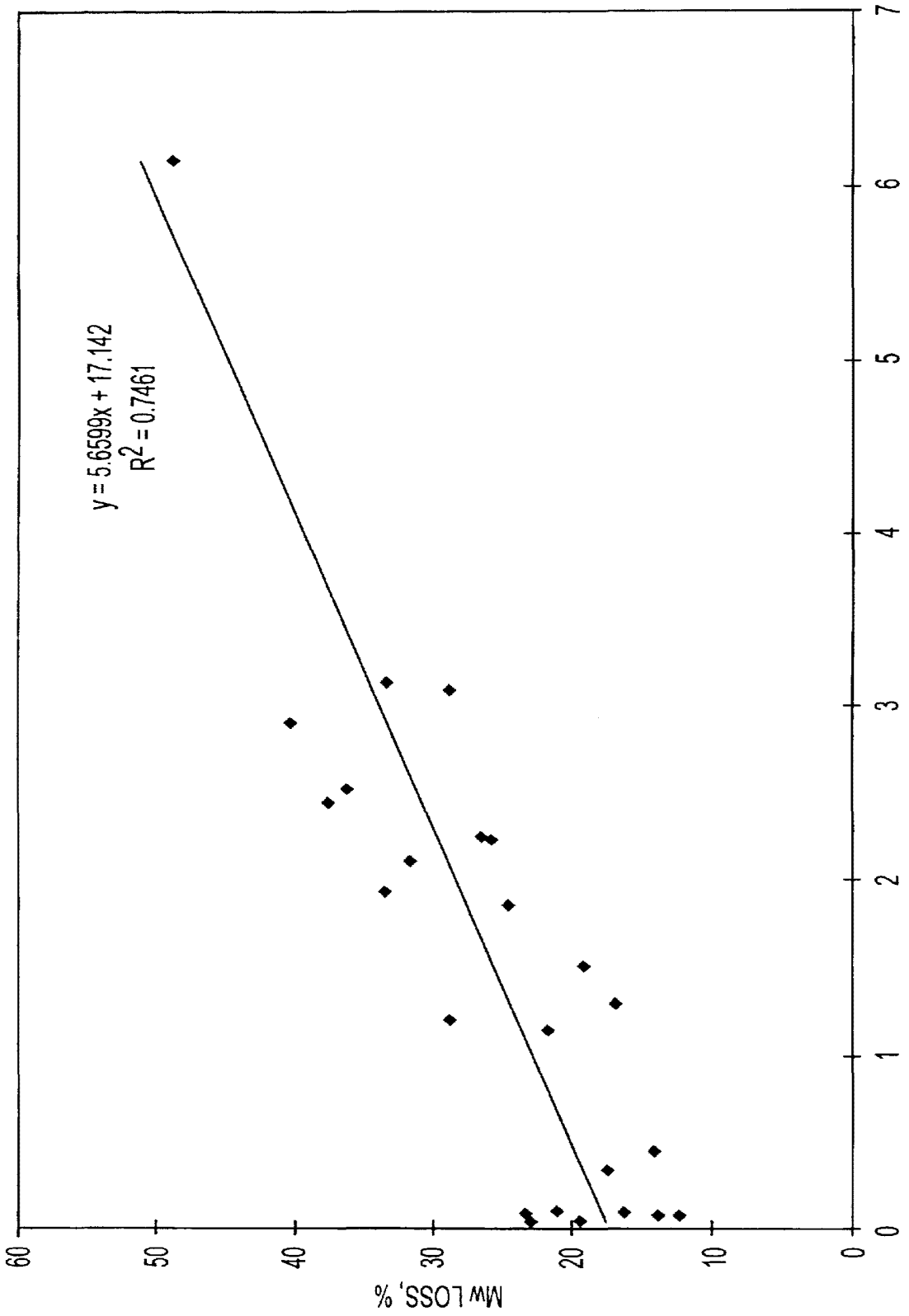

y = 5.6599x + 17.142
R2 = 0.7461
MW LOSS, %
TIME, HRS
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7

FIG. 1

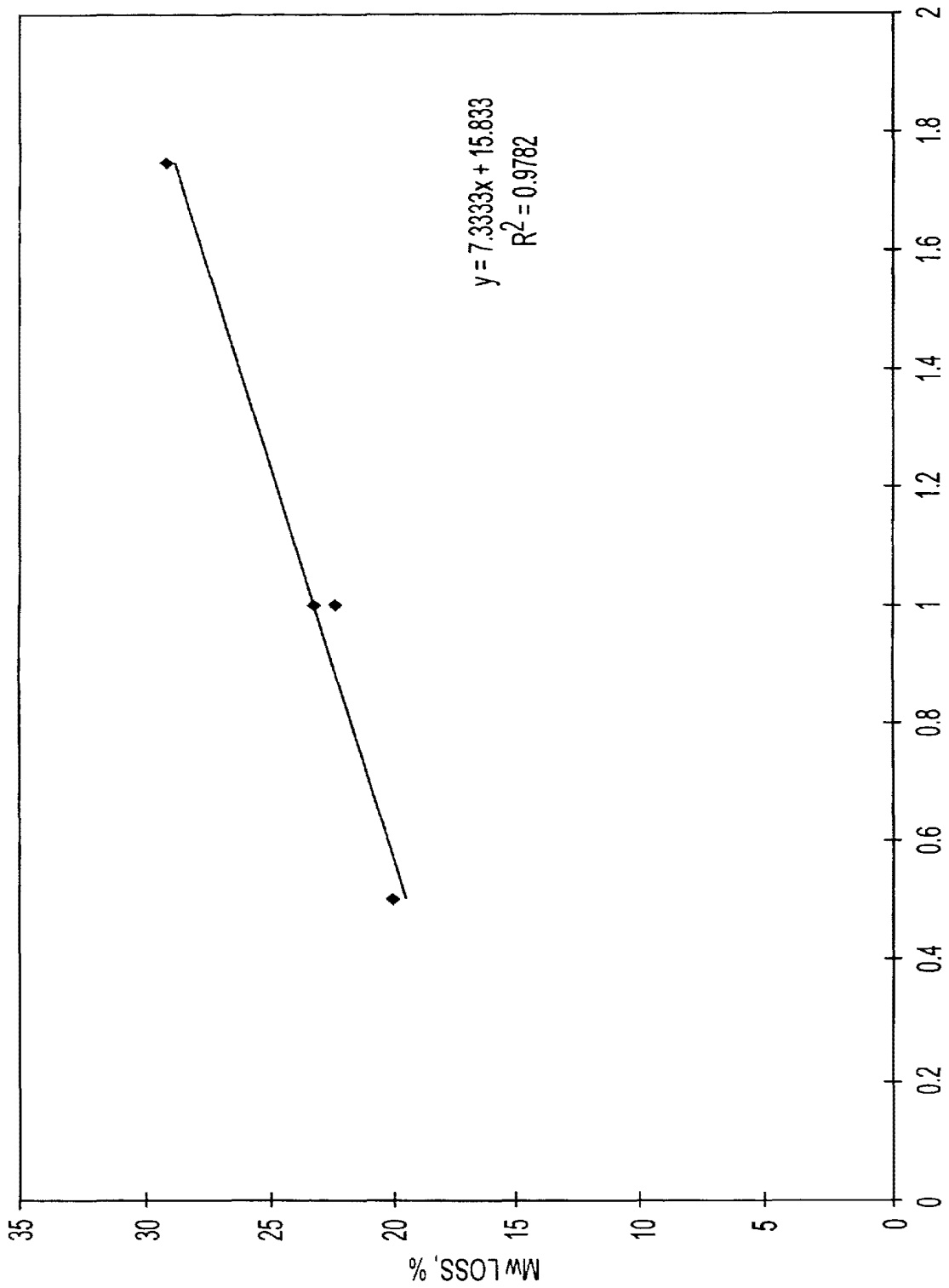

y = 7.3333x + 15.833
R2 = 0.9782
MW LOSS, %
TIME, HRS
0
5
10
15
20
25
30
35
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2

FIG. 2

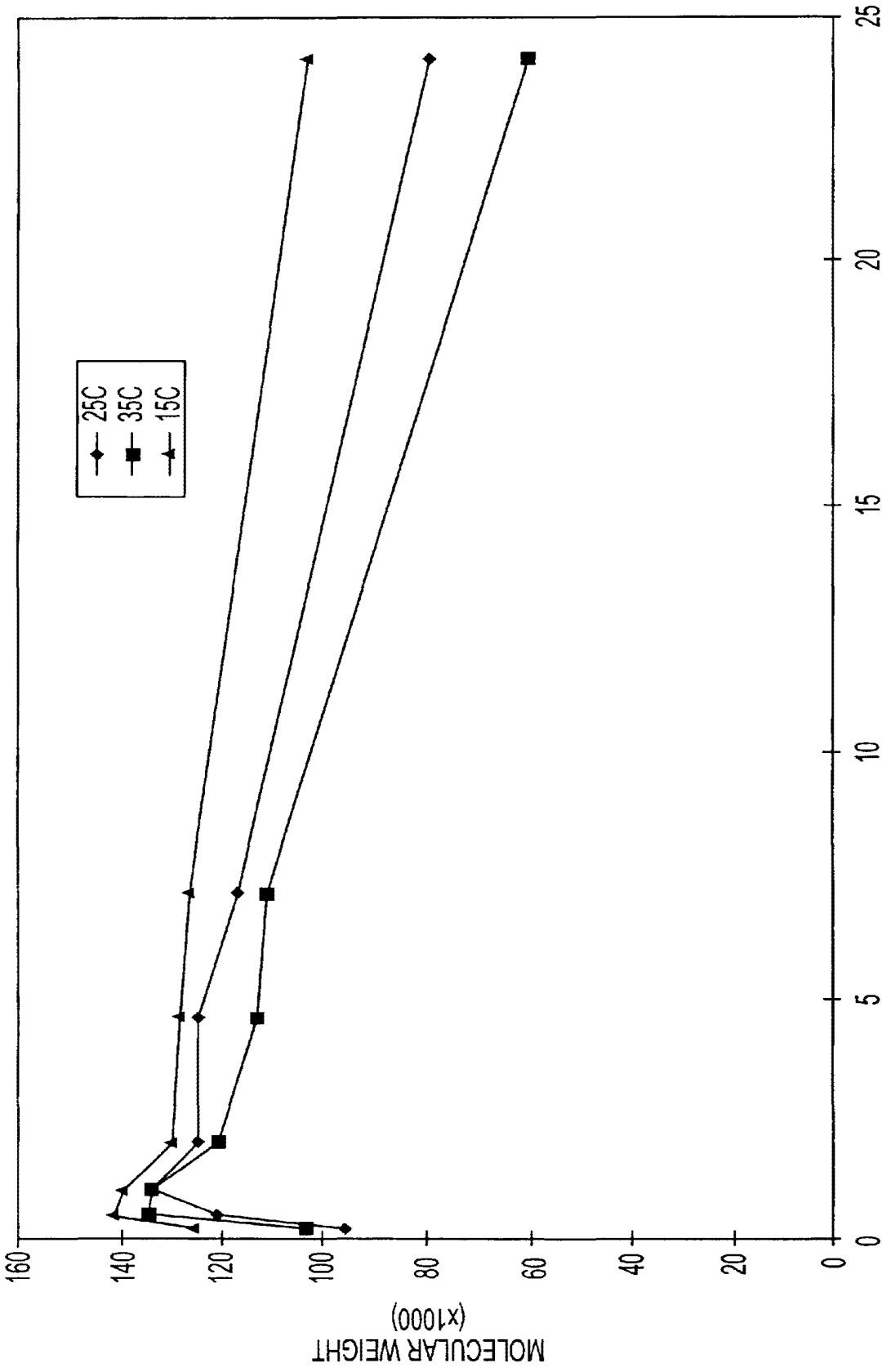

25C
35C
15C
MOLECULAR WEIGHT
(x1000)
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
TIME(HOURS)

FIG. 3

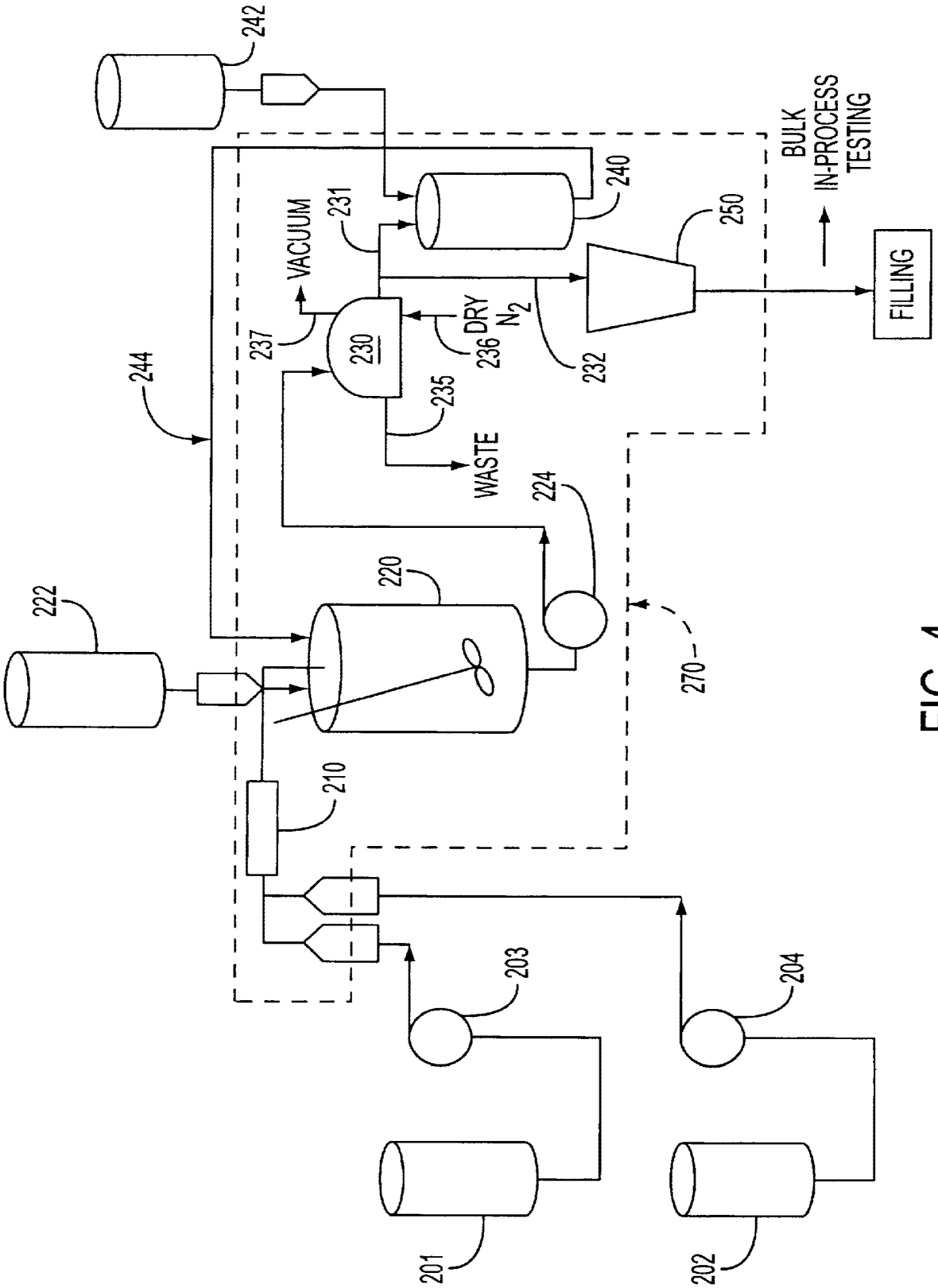

242
BULK
IN-PROCESS
TESTING
240
231
VACUUM
250
FILLING
237
230
DRY
N_2
236
232
244
235
WASTE
224
220
222
270
210
203
204
201
202

FIG. 4

METHOD FOR PREPARING MICROPARTICLES HAVING A SELECTED POLYMER MOLECULAR WEIGHT

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to preparation of microparticles. More particularly, the present invention relates to a method and an apparatus for preparing microparticles having a selected polymer molecular weight.

2. Related Art

A variety of methods is known by which compounds can be encapsulated in the form of microparticles. It is particularly advantageous to encapsulate a biologically active or pharmaceutically active agent within a biocompatible, biodegradable wall forming material (e.g., a polymer) to provide sustained or delayed release of drugs or other active agents. In these methods, the material to be encapsulated (drugs or other active agents) is generally dissolved, dispersed, or emulsified, using stirrers, agitators, or other dynamic mixing techniques, in one or more solvents containing the wall forming material. Solvent is then removed from the microparticles and thereafter the microparticle product is obtained.

One variable that affects the in vitro and in vivo performance of the microparticle product is the molecular weight of the polymer or polymeric matrix material in the final microparticle product. Molecular weight affects drug release characteristics. The molecular weight of a polymer influences the biodegradation rate of the polymer. For a diffusional mechanism of active agent release, the polymer should remain intact until all of the active agent is released from the microparticles, and then degrade. The active agent can also be released from the microparticles as the polymeric matrix material bioerodes. By an appropriate selection of polymeric materials a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties. This is useful in affording multiphasic release patterns.

It has been reported that the molecular weight of the poly(D,L-lactide) ("DL-PL") component of microcapsules containing up to 50% thioridazine free base decreased during fabrication, and in dissolution rate studies of the microcapsule (see Maulding, H.V. et al., Biodegradable Microcapsules: "Acceleration of Polymeric Excipient Hydrolytic Rate by Incorporation of a Basic Medicament", Journal of Controlled Release, Volume 3, 1986, pages 103–117; hereinafter "the Maulding article"). The results reported in the Maulding article reveal that the degradation rate of DL-PL in ketotifen free base microcapsules was greater when the encapsulation process was carried out at 4° C. than it was when the encapsulation process was carried out at 25° C. In contrast, the degradation rate of DL-PL in thioridazine free base microcapsules was greater when the encapsulation process was carried out at 23° C. than it was when the encapsulation process is carried out at 4° C. Based on these results, the Maulding article suggests circumventing the polymer degradation by carrying out the preparation of microcapsules at 4° C. in the case of thioridazine base. The Maulding article does not provide a method by which the molecular weight of the polymer in the finished microparticle can be conveniently controlled. Nor does the Maulding article provide a method for preparing microparticles that have a selected polymer molecular weight in the finished microparticle product.

Thus, there is a need in the art for an improved method for preparing microparticles that controls the molecular weight of the polymer or polymeric matrix material in the finished microparticle product. There is a particular need in the art for an improved process that provides a method for preparing microparticles that have a selected polymer molecular weight. The present invention, the description of which is fully set forth below, solves the need in the art for such an improved method.

SUMMARY OF THE INVENTION

The present invention relates to a method for preparing microparticles. The present invention allows microparticle products of varying polymer molecular weights to be produced using the same molecular weight starting material. The present invention also allows microparticle products with substantially the same polymer molecular weight to be produced from starting materials of varying molecular weight. In one aspect of the invention, a method of preparing microparticles having a selected microparticle polymer molecular weight is provided. The method comprises:

(a) preparing a first phase, the first phase comprising a nucleophilic compound, a polymer having a starting molecular weight, and a solvent for the polymer;

(b) combining the first phase with a second phase under the influence of mixing means to form an emulsion;

(c) combining the emulsion and an extraction medium, thereby forming microparticles; and

(d) maintaining the first phase at a hold temperature for a hold period prior to step (b), the hold period of sufficient duration to allow the starting molecular weight of the polymer to reduce so that the selected microparticle polymer molecular weight is achieved.

In a further aspect of the present invention, another method for preparing microparticles is provided. The method comprises:

(a) providing a polymer having a starting molecular weight;

(b) dissolving the polymer and a nucleophilic compound in a solvent to form a first phase;

(c) combining the first phase with a second phase under the influence of mixing means to form an emulsion;

(d) combining the emulsion and an extraction medium, thereby forming microparticles; and

(e) maintaining the first phase at a hold temperature for a hold period prior to step (c), wherein the hold period is selected so that the starting molecular weight reduces so that a selected microparticle polymer molecular weight is achieved.

In other aspects of the present invention, the foregoing methods comprise adding an active agent to the first phase. In yet further aspects of the present invention, the foregoing methods comprise adding an inactive agent to the first phase.

In further aspects of the invention, the hold temperature is increased, thereby increasing the molecular weight decay of the polymer to reduce the duration of the hold period. The hold temperature can be decreased, thereby decreasing the molecular weight decay of the polymer to increase the duration of the hold period.

Other aspects of the present invention include a microencapsulated active agent and microparticles prepared by the methods of the present invention.

Features and Advantages

It is a feature of the present invention that it can be used to prepare microparticles, including microparticles containing an active agent.

It is a further feature of the present invention that it allows the hold time and temperature of a nucleophilic compound/

polymer solution to be modified to achieve a selected polymer molecular weight in the microparticle product.

An advantage of the present invention is that a selected polymer molecular weight can be achieved in the microparticle product by using a variety of polymers, having varying starting molecular weights, by varying the hold time of the nucleophilic compound/polymer solution.

A further advantage of the present invention is that microparticle products of varying polymer molecular weights can be produced using the same starting polymer, or using a polymer having the same starting molecular weight.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is described with reference to the accompanying drawings. In the drawings, like reference numbers indicate identical or functionally similar elements.

FIG. **1** depicts a graph of molecular weight loss percentage as a function of solution hold time (hours) at a 1 kg scale;

FIG. **2** depicts a graph of molecular weight loss percentage as a function of solution hold time (hours) at a 20 kg scale;

FIG. **3** depicts a graph of molecular weight (kD) as a function of solution hold time (hours) at 15° C., 25° C., and 35° C.; and

FIG. **4** shows one embodiment of an equipment configuration suitable for preparing microparticles in accordance with the present invention.

DETAILED DESCRIPTION OF THE DRAWINGS

Overview

The present invention provides an improved method for preparing microparticles. The methods of the present invention control the hold time and temperature of a polymer solution in order to control the molecular weight of the polymer in the finished microparticle product. In this manner, the methods of the present invention advantageously allow a selected polymer molecular weight to be achieved from a variety of starting material molecular weights. Alternatively, microparticle products of varying polymer molecular weights can be produced using the same molecular weight starting material. Thus, a range of products can be made from the same starting materials, thereby eliminating the need to reformulate the finished product to achieve the desired molecular weight of the polymer in the finished product.

The polymer solution used in the present invention comprises a nucleophilic compound. As used herein, "nucleophilic compound" refers to a compound that promotes by nucleophilic catalysis the ester hydrolysis, such as the polymer scission, that occurs in the biodegradation of biodegradable polymers, such as polymers comprising varying lacotide:glycolide ratios. A nucleophilic compound is a more effective nucleophile toward an ester group of the polymer than hydroxide ion or water. Nucleophilic compounds that catalyze the polymer hydrolysis include, but are not limited to, amines and carboxylate anions, and can be "active agents" (defined below) or "inactive agents" that are not active agents. Examples of nucleophilic compounds that are active agents include, but are not limited to, risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts of the foregoing, naltrexone, and oxybutynin. Examples of nucleophilic compounds that are inactive agents include, but are not limited to, protamine sulfate, spermine, choline, ethanolamine, diethanolamine, and triethanolamine. It should be readily apparent to be one skilled in the art that the present invention is not limited to any particular nucleophilic compound, and that the present invention encompasses other nucleophilic active agents and nucleophilic inactive agents.

To ensure clarity of the description that follows, the following definitions are provided. By "microparticles" or "microspheres" is meant particles that comprise a polymer that serves as a matrix or binder of the particle. The microparticle may contain an active agent or other substance dispersed or dissolved within the polymeric matrix. The polymer is preferably biodegradable and biocompatible. By "biodegradable" is meant a material that should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body. By "biocompatible" is meant not toxic to the body, is pharmaceutically acceptable, is not carcinogenic, and does not significantly induce inflammation in body tissues. As used herein, "body" preferably refers to the human body, but it should be understood that body can also refer to a non-human animal body. By "weight %" or "% by weight" is meant parts by weight per total weight of microparticle. For example, 10 wt. % active agent would mean 10 parts active agent by weight and 90 parts polymer by weight. By "controlled release microparticle" or "sustained release microparticle" is meant a microparticle from which an active agent or other type of substance is released as a function of time. By "mass median diameter" is meant the diameter at which half of the distribution (volume percent) has a larger diameter and half has a smaller diameter.

By "active agent" is meant an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically and pharmacologically active substance that produces a localized or systemic effect in a patient. Such active agents include antibiotics, antiviral agents, anepileptics, analgesics, anti-asthmatics, anti-inflammatory agents and bronchodilators, and may be inorganic and organic compounds, including, without limitation, drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, polysaccharides, steroids, hypnotics and sedatives, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatories, muscle contractants, antimicrobials, antimalarials, hormonal agents including contraceptives, sympathomimetics, polypeptides and proteins capable of eliciting physiological effects, diuretics, lipid regulating agents, antiandrogenic agents, leukotriene antagonists, antiparasites, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, fats, ophthalmics, antienteritis agents, electrolytes and diagnostic agents.

Method and Examples

The following examples are provided to explain the invention, and to describe the materials and methods used in carrying out the invention. The examples are not intended to limit the invention in any manner.

Molecular Weight Experiments with Nucleophilic Compounds

EXAMPLE 1

A series of experiments were conducted at the 1 kg scale that demonstrate the relationship between molecular weight of the finished microparticle product, and the duration of a hold period of a nucleophilic compound/polymer solution. Microparticles comprising risperidone were prepared at the one-kilogram scale. The 1 Kg process (400 grams of active agent and 600 grams of polymer) provides a theoretical drug loading of the microparticles of 40% (400 grams/1000 grams×100%).

A 16.7 wt. % polymer solution was prepared by dissolving 600 grams of MEDISORB® 7525 DL polymer (Alkermes, Inc., Blue Ash, Ohio) in ethyl acetate. A 24 wt. % drug solution was prepared by dissolving 400 grams of risperidone (basic nucleophilic active agent) (Janssen Pharmaceutica, Beerse, Belgium) in benzyl alcohol. A nucleophilic active agent/polymer solution (organic phase) was prepared by mixing the drug solution into the polymer solution. The active agent/polymer solution was maintained at a temperature of 25±5° C. The active agent/polymer solution is held for a hold time of sufficient duration to achieve the selected or desired polymer molecular weight in the finished microparticle product, based on the starting molecular weight of the polymer. The results of the experiments, showing the effect of hold time on molecular weight loss, are discussed in more detail below with respect to Table 1 and FIG. **1**.

The second, continuous phase was prepared by preparing a 30 liter solution of 1% polyvinyl alcohol (PVA), the PVA acting as an emulsifier. To this was added 2086 grams of ethyl acetate to form a 6.5 wt. % solution of ethyl acetate.

The two phases were combined using a static mixer, such as a ½" Kenics static mixer available from Chemineer, Inc., North Andover, Mass. A total flow rate of 3 L/min generally provides microparticle size distributions with a mass median diameter (MMD) in the range of about 80–90μ. The ratio of continuous phase to discontinuous phase was 5:1 (v/v).

The quench liquid was 2.5% solution of ethyl acetate and water-for-injection (WFI) at 5–10° C. The volume of the quench liquid is 0.25L per gram of batch size. The quench step was carried out for a time period greater than about 4 hours, with stirring of the microparticles in the quench tank.

After completion of the quench step, the microparticles were collected, de-watered, and dried. The temperature was maintained at less than about 15° C.

The microparticles were then re-slurried in a re-slurry tank using a 25% ethanol solution. The temperature in the re-slurry tank was in the range of about 0° C. to about 15° C. The microparticles were then transferred back to the quench tank for washing for a time period of at least 6 hours with another extraction medium (25% ethanol solution) that was maintained at preferably 25°±1° C.

The microparticles were collected, de-watered, and dried. The temperature was warmed to greater than about 20° C. but below 40° C. Drying continued for a time period greater than about 16 hours.

Twenty-four batches of risperidone microparticles at the 1 kg scale were prepared using the process described above. Table 1 below shows, for each batch, the starting molecular weight of the polymer (kD), the final molecular weight of the polymer in the finished microparticle product (kD), the percent loss in molecular weight of the polymer, and the hold time (hours) of the active agent/polymer solution. The molecular weight of the polymer in the finished microparticle product was determined by GPC.

TABLE 1

Batch#	Starting Mw kD	Final Mw kD	% Loss	Hold time Hours
825	230	182	21.0	0.10
708	161	110	32.0	2.08
714	161	133	17.3	0.33
812	161	100	37.9	2.40
819	161	102	36.7	2.47
319	131	110	16.2	0.10
331	131	115	12.2	0.07
423	131	78	40.7	2.85
506	129	112	13.6	0.07
512	129	86	33.7	3.10
520	129	92	29.1	3.07
527	129	95	26.8	2.22
603	129	65	49.4	6.10
610	129	101	22.0	1.13
617	128	95	26.1	2.20
902	128	85	33.8	1.90
908	128	91	29.0	1.18
921	128	99	23.2	0.08
930	128	103	19.4	0.03
915	92	69	24.8	1.82
1021	135	104	23.0	0.03
1028	138	119	13.7	0.45
1110	138	115	16.8	1.28
1215	138	111	19.4	1.50

The data reported in Table 1 is depicted in the graph shown in FIG. **1**. FIG. **1** shows an initial loss in molecular weight of approximately 17%, with an additional loss of approxamately 5.7% per hour of hold time of the active agent/polymer solution.

EXAMPLE 2

Additional experiments were conducted at the 20 kg scale that also demonstrate the relationship between molecular weight of the finished microparticle product, and the duration of a hold period of a nucleophilic compound/polymer solution. Microparticles comprising risperidone were prepared at the twenty-kilogram scale. The 20 Kg process (8 kg of active agent and 12 kg of polymer) provides a theoretical drug loading of the microparticles of 40% (8 kg/20 kg×100%).

A 16.7 wt. % polymer solution was prepared by dissolving 12 kg of MEDISORB® 7525 DL polymer (Alkermes, Inc., Blue Ash, Ohio) in ethyl acetate. A 24 wt. % drug solution was prepared by dissolving 8 kg of risperidone (Janssen Pharmaceutica, Beerse, Belgium) in benzyl alcohol. A nucleophilic active agent/polymer solution (organic phase) was prepared by mixing the drug solution into the polymer solution. The active agent/polymer solution was maintained at a temperature of 25±5° C. The active agent/polymer solution is held for a hold time of sufficient duration to achieve the selected or desired polymer molecular weight in the finished microparticle product, based on the starting molecular weight of the polymer. The results of the experiments, showing the effect of hold time on molecular weight loss, are discussed in more detail below with respect to Table 2 and FIG. **2**.

The second, continuous phase was prepared by preparing a 600 liter solution of 1% PVA, the PVA acting as an emulsifier. To this was added 42 kg of ethyl acetate to form a 6.5 wt. % solution of ethyl acetate. The two phases were combined using a static mixer, such as a 1" Kenics static mixer available from Chemineer, Inc., North Andover, Mass.

The quench liquid was 2.5% solution of ethyl acetate and water-for-injection (WFI) at 5–10° C. The volume of the quench liquid is 0.25L per gram of batch size. The quench step was carried out for a time period greater than about 4 hours, with stirring of the microparticles in the quench tank.

After completion of the quench step, the microparticles were collected, de-watered, and dried. The temperature was maintained at less than about 15° C.

The microparticles were then re-slurried in a re-slurry tank using a 25% ethanol solution. The temperature in the re-slurry tank was in the range of about 0° C. to about 15% microparticles were then transferred back to the quench tank for washing for a time period of at least 6 hours with another extraction medium (25% ethanol solution) that was maintained at preferably 25°±1° C.

The microparticles were collected, de-watered, and dried. The temperature was greater than about 20° C. but below 40° C. Drying continued for a time period about 16 hours.

Four batches of risperidone microparticles at the 20 kg scale were prepared using the process described above. Table 2 below shows, for each batch, the starting molecular wieght of the polymer (kD), the final molecular weight of the polymer in the finished microparticle product (kD), the percent loss in molecular weight of the polymer, and the hold time hours) of the active agent/polymer solution. The molecular weight of the polymer in the finished microparticle product was determined by GPC.

TABLE 2

Batch#	Starting Mw kD	Final Mw kD	% Loss	Hold time hours
3308	146	117	20	0.5
4068	145	103	29	1.75
4138	143	111	22	1.0
4208	143	110	23	1.0

The data reported in Table 2 show that from a relatively constant molecular wieght starting material (143 kD, 145 kD, and 146 kD), a variable finished microparticle product molecular weight was achieved by varying the hold time of the active agent/polymer solution hold time. The data reported in Table 2 is depicted in the graph shown in FIG. **2**. FIG. **2** shows an initial loss in molecular weight of approximately 16%, with an additional loss of approximately 7.3% per hour of hold time of the active agent/polymer solution.

EXAMPLE 3

The starting molecular weight of the polymer (kD) and the final molecular weight of the polymer in a finished microparticle product (kD) was determined for microparticles containing the nucleophilic compound naltrexone. The starting polymer lactide:glycolide ratio was 75:25, 85:15, and 65:35. The polymers used were MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6535 DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio.

The naltrexone base microparticles were produced using a co-solvent extraction process. The theoretical batch size was 15 to 20 grams. The polymer was dissolved in ethyl acetate to produce a 16.7% w/w polymer solution. The naltrexone base anhydrous was dissolved in benzyl alcohol to produce a 30.0% w/w solution. In various batches, the amount of drug and polymer used was varied to produce microparticles with different theoretical drug loading ranging from 30%–75%. The ambient polymer and drug solutions were mixed together until a single homogeneous solution (organic phase) was produced. The aqueous phase was at ambient conditions and contained 1% w/w polyvinyl alcohol and a saturating amount of ethyl acetate. These two solutions were pumped via positive displacement pumps at a ratio of 3:1 (aqueous:organic) through a ¼" in-line mixer to form an emulsion. The emulsion was transferred to a stirring solvent extraction solution consisting of 2.5% w/w of ethyl acetate dissolved in distilled water at 5–10° C. and at a volume of 0.5L of extraction solution per theoretical gram of microparticles. Both the polymer and drug solvents were extracted into the extraction solution from the emulsion droplets to produce microparticles. The initial extraction process ranged from two to four hours. The microparticles were collected on a 25 μm sieve and rinsed with a cold (<5° C.) 25% w/w ethanol solution. The microparticles were dried cold overnight (approximately 17 hours) using nitrogen. The microparticles were then transferred to the reslurry solution, which consisted of a vigorously stirring 25% w/w ethanol solution at 5–10° C. After a short mixing time (five to fiffteen minutes), the reslurry solution and the microparticles were transferred to a stirring 25% w/w ethanol secondary extraction solution (approximately 25° C. at a volume of 0.2 L of secondary extraction solution per theoretical gram of microparticles). The microparticles stirred for six hours enabling additional solvent removal from the microparticles to take place. The microparticles were then collected on a 25 μm sieve and rinsed with a 25% w/w ethanol solution at ambient temperature. These microparticles dried in a hood under ambient conditions overnight (approximately 17 hours), were sieved to remove agglomerated microparticles and then placed into a freezer for storage.

As shown below in Table 3, three batches of microparticles were prepared using the 75:25 polymer, two batches for the 85:15 polymer, and four batches for the 65:35 polymer. For each batch, Table 3 shows the starting molecular weight of the polymer (kD), and the final molecular weight of the polymer in the finished microparticle products (kD), and the percent loss in molecular weight of the polymer. The molecular weight of the polymer in the finished microparticle product was determined by GPC. The data in Table 3 provides an example of the loss in molecular weight of the polymer in a finished microparticle product containing a nucleophilic compound (naltrexone) for polymers having varying lactide:glycolide ratios.

TABLE 3

Starting Polymer Lactide:glycolide ratio	Batch	Starting Mw kD	Final Mw kD	% Loss
75:25	99-123-004	116.2	76.0	34.6
	99-123-009	116.2	74.0	36.3
	99-123-012	116.2	74.3	36.1
85:15	99-123-016	109.7	83.7	23.7
	99-123-024	109.7	74.9	31.7
65:35	99-123-021	102.3	56.3	45.0
	99-123-028	102.3	63.4	38.0
	99-123-037	102.3	69.6	32.0
	99-123-034	102.3	79.6	22.2

EXAMPLE 4

Additional experiments were conducted with other polymers that also demonstrate the relationship between molecular weight of the finished microparticle product, and the duration of a hold period of a nucleophilic compound/

polymer solution. Microparticles comprising other polymers having different lactide:glycolide ratios were prepared. Microparticles comprising risperidone using polymers having lactide:glycolide ratios of 65:35, 85:15, and 100:0 were prepared at the 1 Kg scale using the same process described above in Example 1. The polymers used were MEDISORB® 6535 DL polymer, MEDISORB® 8515 DL polymer, and MEDISORB® 100 DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio.

Table 4 below shows, for each polymer, the starting molecular weight of the polymer (kD), the final molecular weight of the polymer in the finished microparticle product (kD), the percent loss in molecular weight of the polymer, and the hold time (hours) of the active agent/polymer solution. The molecular weight of the polymer in the finished microparticle product was determined by GPC.

TABLE 4

Lactide:glycolide ratio	Starting Mw kD	Final Mw kD	% Loss	Hold time hours
65:35	105	79	24.8	0.27
85:15	112	96	14.3	0.23
100 dl	105	98	6.7	0.17

The data reported in Table 4 show that a microparticle product having about the same molecular weight (96 kD and 98 kD) can be prepared from two different molecular weight polymers (112 kD and 105 kD, respectively) having two different lactide:glycolide ratios (85:15 and 100:0, respectively). The present invention thus advantageously allows microparticle products with the same polymer molecular weight to be produced using two different starting materials.

EXAMPLE 5

Additional experiments were conducted that demonstrate the molecular weight loss of polymers in the presence of a nucleophilic compound (oxybutynin) as a function of time. Tests were conducted using a 100:0 lactide:glycolide polymer and two 75:25 lactide:glycolide polymers with differing inherent viscosity. For each test, the following protocol was carried out. Weigh about 6 g polymer into an Erlenmeyer flask. Add to the polymer 44 g ethyl acetate, sonicate and shake to dissolve the polymer. Weigh 1.5 g oxybutynin base. Stir the polymer solution, and add the drug to the polymer solution. Start the timer as the drug is added. Sample the drug/polymer solution at 1, 5 and 15 minutes, taking about ⅓ of the original volume for each aliquot as the solution stirs. Dispense the aliquot into 250 mL 50:50 H_2O:MeOH, and stir. This mix precipitates the polymer and removes the drug from the precipitate. Allow precipitated polymer to settle and decant the supernatant. Wash polymer residue with 100mL MeOH, stir approximately one minute, add up to 250 mL H_2O. Allow polymer to settle again, and repeat. Residue is then removed from the beaker and placed in a scintillation vial and frozen. Once all samples are collected and frozen, all samples are placed in a lyophilizer, cooled to −10° C. The lyophilizer is activated, and once a stable vacuum is achieved, the shelf temperature is raised to 15° C. and held overnight (~18 hours) to remove residual solvents.

The results of these experiments are shown in Table 5. For each experiment, the starting molecular weight of the polymer is shown, along with the polymer molecular weight at 1, 5, and 15 minutes of exposure of the polymer to the nucleophilic compound in the drug/polymer solution. As can be seen in Table 5, the longer the exposure or hold time of the drug/polymer solution, the lower the molecular weight of the polymer.

TABLE 5

Starting Polymer Lactide: glycolide ratio	Starting Mw, kD	Time = 1 min Mw, kD	Time = 5 min Mw, kD	Time = 15 min Mw, kD
100:0	77.1	67.2	63	60.8
75:25	82.8	56.2	55.1	48.8
75:25	54.1	44.1	42.9	38.4

Molecular Weight Temperature Experiments

EXAMPLE 6

Additional experiments were conducted to determine the effect of temperature on the relationship between molecular weight of the finished microparticle product, and the duration of a hold period of a nucleophilic compound/polymer solution. Fifty grams of risperidone (Janssen Pharmaceutica, Beerse, Belgium) were dissolved in 275 g of benzyl alcohol to form a drug solution. A polymer solution was formed by dissolving 75 g of MEDISORB® 7525 DL polymer (Alkerrnes, Inc., Blue Ash, Ohio) in ethyl acetate. The starting molecular weight of the polymer was 146 kD. The drug solution and the polymer solution were mixed to form a combined solution. A flask of the combined solution was placed in each of a 15° C., 25° C., and 35° C. chamber. At periodic time intervals, 10 cc of the combined solution was withdrawn from the flask in each chamber via a syringe and needle. The 10 cc sample was then precipitated in a bath containing 200 ml methanol at room temperature (approximately 20° C.). The polymeric precipitate was recovered from the methanol bath, and vacuum dried overnight. The dried samples were tested for their molecular weight by GPC.

The results of the experiments are depicted in the graph of FIG. **3**. As shown in FIG. **3**, the molecular weight decay increases as temperature increases. Therefore, by increasing the hold temperature of the solution containing the polymer and the nucleophilic compound, the molecular weight decay of the polymer increases, and the duration of the hold period to achieve a particular molecular weight reduction is reduced. Similarly, by decreasing the hold temperature of the solution containing the polymer and the nucleophilic compound, the molecular weight decay of the polymer decreases, and the duration of the hold period to achieve a particular molecular weight reduction is increased. For example, the time required to reduce the molecular weight form 130 kD to 110 kD is the shortest at 35° C. (about 5 hours) and the longest at 15° C. (about 15 hours).

FIG. **3** shows an initial increase in polymer molecular weight. This phenomenon is most likely occurring because some portion of the polymer, particularly the lower molecular weight fractions is soluble in the extraction medium. Because the analytical measurement of molecular weight is a representation of all the molecular weight fractions present, removing (dissolving) the low molecular weight material can increase the measured molecular weight.

Methods of Preparing Microparticles

EXAMPLE 7

As exemplified by the examples discussed above, methods for preparing microparticles having a selected micro-

particle polymer molecular weight in accordance with the present invention will now be described in more detail. In one embodiment of the present invention, a first phase, comprising a nucleophilic compound, a polymer having a starting molecular weight, and a solvent for the polymer, is prepared. In one embodiment of the present invention, the first phase is prepared by dissolving a nucleophilic active agent in a first solvent to form an active agent solution. The polymer is dissolved in a second solvent to form a polymer solution. The active agent solution and the polymer solution are blended to form the first phase. In a particularly preferred embodiment, the active agent is selected from the group consisting of risperidone, 9–25 hydroxyrisperidone, and pharmaceutically acceptable salts thereof. In such an embodiment, a preferred first solvent is benzyl alcohol, and a preferred second solvent is ethyl acetate.

In another embodiment of the present invention, the first phase is prepared by dissolving the nucleophilic compound and the polymer in a solvent to form a solution. In yet a further embodiment, an active agent is added to the first phase. In a further embodiment, an inactive agent is added to the first phase. It should be understood that the present invention is not limited to any particular method or process by which the first phase is prepared, and other suitable processes would be readily apparent to one skilled in the art.

A second phase is prepared, and combined with the first phase under the influence of mixing means to form an emulsion. In a preferred embodiment, a static mixer is used to combine the two phases to form an emulsion. A process for forming an emulsion using a static mixer is described, for example, in U.S. Pat. No. 5,654,008, the entirety of which is incorporated herein by reference. The emulsion is combined with an extraction medium that extracts solvent from the emulsion droplets, thereby hardening them into microparticles.

Prior to combining the first and second phases, the first phase is maintained at a hold temperature for a hold period. The hold period is of sufficient duration to allow the starting molecular weight of the polymer to reduce to the selected microparticle polymer molecular weight at the hold temperature. Based on the teachings and examples provided herein, and the knowledge of skilled artisans, the determination of suitable hold temperatures and hold periods is within the routine skill of skilled artisans and would not require undue experimentation. In a preferred embodiment of the present invention, the starting molecular weight of the polymer reduces by about 10% to about 50% to reach the selected polymer molecular weight. However, it should be understood by one skilled in the art that the present invention is not limited to such a percentage reduction.

During the hold period, the first phase may be mixed, stirred, or otherwise agitated. Alternatively, during the hold period, the first phase may be subjected to no mixing, stirring, or agitation. The hold temperature is preferably in the range of from about 15° C. to about 35° C., more preferably about 25° C.

An alternate method for preparing microparticles in accordance with the present invention will now be described. A polymer having a starting molecular weight and a nucleophilic compound are dissolved in a solvent to form a first phase. An active agent and/or an inactive agent can be added to the first phase. The first phase is combined with a second phase under the influence of mixing means to form an emulsion. The emulsion is combined with an extraction medium that extracts solvent, thereby hardening the emulsion droplets into microparticles. Prior to combining the first and second phases, the first phase is maintained at a hold temperature for a hold period. The hold period is selected so that the starting molecular weight of the polymer reduces to a selected microparticle polymer molecular weight at the hold temperature. The duration of the hold period can be adjusted by changing the hold temperature in a manner as described above.

Microparticles of the Present Invention

The microparticles prepared by the process of the present invention preferably comprise a polymeric binder. Suitable polymeric binder materials include poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and polyphosphazines. Poly (d,l-lactic-co-glycolic acid) is commercially available from Alkermes, Inc. (Blue Ash, Ohio). A suitable product commercially available from Alkermes, Inc. is a 50:50 poly(d,l-lactic-co-glycolic acid) known as MEDISORB® 5050 DL. This product has a mole percent composition of 50% lactide and 50% glycolide. Other suitable commercially available products are MEDISORB® 6535 DL, 7525 DL, 8515 DL and poly(d,l-lactic acid) (100 DL). Poly(lactide-co-glycolides) are also commercially available from Boehringer Ingelheim (Germany) under its Resomer® mark, e.g., PLGA 50:50 (Resomer® RG 502), PLGA 75:25 (Resomer® RG 752) and d,l-PLA (Resomer® RG 206), and from Birmingham Polymers (Birmingham, Ala.). These copolymers are available in a wide range of molecular weights and ratios of lactic acid to glycolic acid.

One type of microparticle. suitable for preparation by the present invention is a sustained-release microparticle that is biodegradable. However, it should be understood by one skilled in the art that the present invention is not limited to biodegradable or other types of sustained-release microparticles. As would be apparent to one skilled in the art, the molecular weight of the polymeric binder material for biodegradable microparticles is of some importance. The molecular weight should be high enough to permit the formation of satisfactory polymer coatings, i.e., the polymer should be a good film former. However, since the properties of the film are also partially dependent on the particular polymeric binder material being used, it is very difficult to specify an appropriate molecular weight range for all polymers. The molecular weight of the polymer is also important from the point of view of its influence upon the biodegradation rate of the polymer. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released from the microparticles and then degrade. The drug can also be released from the microparticles as the polymeric binder bioerodes. By an appropriate selection of polymeric materials a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties. This is useful in according multiphasic release patterns. A satisfactory starting molecular weight of the polymer is in the range of 5–500 kD, preferably in the range of from about 50 kD to about 250 kD. The microparticle polymer molecular weight is preferably in the range of from about 10 kD to about 185 kD.

The microparticles prepared in accordance with the present invention may include an active agent or other type of substance that is released from the microparticles into the host. However, it should be understood that the present invention is not limited to preparation of microparticles that

contain an active agent. The active agent can be a nucleophilic compound. Alternatively, the active agent is not a nucleophilic compound and is added to the microparticles during the formation process. Such active agents can include 1,2-benzazoles, more particularly, 3-piperidinyl-substituted 1,2-benzisoxazoles and 1,2-benzisothiazoles. The most preferred active agents of this kind are 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("risperidone") and 3-[2-[4-(6-fluro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("9-hydroxyrisperidone") and the pharmaceutically acceptable salts thereof. Risperidone (which term, as used herein, is intended to include its pharmaceutically acceptable salts) is most preferred. Risperidone can be prepared in accordance with the teachings of U.S. Pat. No. 4,804,663, the entirety of which is incorporated herein by reference. 9-hydroxyrisperidone can be prepared in accordance with the teachings of U.S. Pat. No. 5,158,952, the entirety of which is incorporated herein by reference.

Other biologically active agents include non-steroidal antifertility agents; parasympathomimetic agents; psychotherapeutic agents; tranquilizers; decongestants; sedative hypnotics; steroids; sulfonamides; sympathomimetic agents; vaccines; vitamins; antimalarials; anti-migraine agents; anti-Parkinson agents such as L-dopa; anti-spasmodics; anticholinergic agents (e.g. oxybutynin); antitussives; bronchodilators; cardiovascular agents such as coronary vasodilators and nitroglycerin; alkaloids; analgesics; narcotics such as codeine, dihydrocodienone, meperidine, morphine and the like; non-narcotics such as salicylates, aspirin, acetaminophen, d-propoxyphene and the like; opioid receptor antagonists, such as naltrexone and naloxone; antibiotics such as gentamycin, tetracycline and penicillins; anti-cancer agents; anti-convulsants; anti-emetics; antihistamines; anti-inflammatory agents such as hormonal agents, hydrocortisone, prednisolone, prednisone, non-hormonal agents, allopurinol, indomethacin, phenylbutazone and the like; prostaglandins and cytotoxic drugs.

Still other suitable active agents include estrogens, antibacterials; antifungals; antivirals; anticoagulants; anticonvulsants; antidepressants; antihistamines; and immunological agents.

Other examples of suitable biologically active agents include peptides and proteins, analogs, muteins, and active fragments thereof, such as immunoglobulins, antibodies, cytokines (e.g. lymphokines, monokines, chemokines), blood clotting factors, hemopoietic factors, interleukins (IL-2, IL-3, IL-4, IL-6), interferons (β-IFN, α-IFN and γ-IFN), erythropoietin, nucleases, tumor necrosis factor, colony stimulating factors (e.g., GCSF, GM-CSF, MCSF), insulin, enzymes (e.g., superoxide dismutase, tissue plasminogen activator), tumor suppressors, blood proteins, hormones and hormone analogs (e.g., growth hormone, adrenocorticotropic hormone and luteinizing hormone releasing hormone (LHRH)), vaccines (e.g., tumoral, bacterial and viral antigens); somatostatin; antigens; blood coagulation factors; growth factors (e.g., nerve growth factor, insulin-like growth factor); protein inhibitors, protein antagonists, and protein agonists; nucleic acids, such as antisense molecules; oligonucleotides; and ribozymes. Small molecular weight agents suitable for use in the invention include, antitumor agents such as bleomycin hydrochloride, carboplatin, methotrexate and adriamycin; antipyretic and analgesic agents; antitussives and expectorants such as ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride and codeine phosphate; sedatives such as chlorpromazine hydrochloride, prochlorperazine hydrochloride and atropine sulfate; muscle relaxants such as tubocurarine chloride; antiepileptics such as sodium phenytoin and ethosuximide; antiulcer agents such as metoclopramide; antidepressants such as clomipramine; antiallergic agents such as diphenhydramine; cardiotonics such as theophillol; antiarrhythmic agents such as propranolol hydrochloride; vasodilators such as diltiazem hydrochloride and bamethan sulfate; hypotensive diuretics such as pentolinium and ecarazine hydrochloride; antidiuretic agents such as metformin; anticoagulants such as sodium citrate and heparin; hemostatic agents such as thrombin, menadione sodium bisulfite and acetomenaphthone; antituberculous agents such as isoniazide and ethanbutol; hormones such as prednisolone sodium phosphate and methimazole.

The microparticles can be mixed by size or by type. However, it should be understood that the present invention is not limited to the use of biodegradable or other types of microparticles that contain an active agent. In one embodiment, the microparticles are mixed in a manner that provides for the delivery of active agent to the host in a multiphasic manner and/or in a manner that provides different active agents to the host at different times, or a mixture of active agents at the same time. For example, secondary antibiotics, vaccines, or any desired active agent, either in microparticle form or in conventional, unencapsulated form can be blended with a primary active agent and provided to the host.

Apparatus

With reference now to FIG. **4**, one embodiment is shown of an equipment configuration suitable for use in preparing microparticles in accordance with the present invention. In a preferred embodiment of the present invention, the equipment contained within the dotted line boundary shown generally at **270** is sterilized using a "steam-in-place" (SIP) process.

A first phase **201** is provided. First phase **201** is preferably the discontinuous phase, comprising a polymer dissolved in one or more solvents, and an active agent. The active agent can be dissolved or dispersed in the same or a different solvent than the solvent(s) in which the polymer is dissolved. A second phase **202** is preferably the continuous phase, preferably comprising water as the continuous processing medium. Preferably, an emulsifying agent such as a surfactant or a hydrophilic colloid is added to the continuous phase to prevent the microdroplets from agglomerating and to control the size of the microdroplets in the emulsion. Examples of compounds that can be used as surfactants or hydrophilic colloids include, but are not limited to, poly (vinyl alcohol) (PVA), carboxymethyl cellulose, gelatin, poly(vinyl pyrrolidone), Tween 80, Tween 20, and the like. The concentration of surfactant or hydrophilic colloid in the continuous phase will be from about 0.1% to about 10% by weight based on the continuous processing medium, depending upon the surfactant, hydrophilic colloid, the discontinuous phase, and the continuous processing medium used. A preferred continuous phase is 0.1 to 10 wt. %, more preferably 0.5 to 2 wt. %, solution of PVA in water. Although not absolutely necessary, it is preferred to saturate the continuous phase with at least one of the solvents forming the discontinuous phase.

First phase **201** and second phase **202** are combined under the influence of mixing means to form an emulsion. A preferred type of mixing means is a static mixer **210**. Other mixing means suitable for use with the present invention include, but are not limited to, devices for mechanically agitating the first and second phases, such as homogenizers, propellers, impellers, stirrers, and the like.

Preferably, the discontinuous and continuous phases **201** and **202** are pumped through static mixer **210** to form an emulsion, and into a large volume of quench liquid, to obtain microparticles containing the active agent encapsulated in the polymeric matrix material. A pump **203** pumps first phase **201** into static mixer **210**, and a pump **204** pumps second phase **202** into static mixer **210**. An especially preferred method of mixing with a static mixer in the process of the present invention is disclosed in U.S. Pat. No. 5,654,008, the entirety of which is incorporated herein by reference.

First and second phases **201** and **202** are mixed in static mixer **210** to form an emulsion. The emulsion formed comprises microparticles containing active agent encapsulated in the polymeric matrix material. The microparticles are then preferably stirred in a quench or extraction tank **220** containing a quench liquid in order to remove most of the solvent from the microparticles, resulting in the formation of hardened microparticles. Following the movement of the microparticles from static mixer **210** and entrance into quench tank **220**, the continuous processing medium is diluted, and much of the solvent in the microparticles is removed by extraction. In this extractive quench step, the microparticles can be suspended in the same continuous phase (second phase **202**) used during emulsification, with or without hydrophilic colloid or surfactant, or in another quench liquid. The quench liquid removes a significant portion of the solvent from the microparticles, but does not dissolve them. During the extractive quench step, the quench liquid containing dissolved solvent can, optionally, be removed and replaced with fresh quench liquid.

Upon completion of the quench step in quench tank **220**, the microparticles are transferred by a pump **224** to a device **230** that functions as a microparticle collecting device, de-watering device, and drying device.

Device **230** comprises a vibrating sieve or screen. The vibration causes smaller particles and liquid to drop through the screen, while larger particles are retained. The smaller particles and liquid that drop through the screen are removed as waste **235**. Device **230** also functions as a vacuum dryer, through the use of a vacuum line **237**. The microparticles are fluidized by the vibrational energy, and by a small amount of a dry gas bleed, preferably a dry nitrogen (N_2) bleed **236**.

The dried microparticles are transferred to another extraction medium to carry out a wash step. The wash step is preferably carried out in quench tank **220**, using an extraction medium **222** having a temperature higher than the glass transition temperature (T_g) of the microparticles. To carry out the wash step, the microparticles are first introduced into a re-slurry tank or other type of vessel **240**, as shown by path **231**. The temperature of the extraction medium **242** that is used in vessel **240** is lower than the T_g of the microparticles.

After the wash step is completed in quench tank **220**, the microparticles are again transferred via pump **224** into device **230** for de-watering and final drying. At the completion of final drying, the microparticles are discharged from device **230** in the manner described above into a sifter **250**, as shown by path **232**. Sifter **250** is used to fractionate the microparticles by size for filling into vials and for bulk in-process testing (e.g., aspect, active agent content, residual solvents, in vitro release, and particle size distribution).

Conclusion

While various embodiments of the present invention have been described above, it should be understood that they have been presented by way of example only, and not limitation. The present invention is not limited to the preparation of controlled release microparticles or microparticles containing an active agent, nor is it limited to a particular active agent, polymer or solvent, nor is the present invention limited to a particular scale or batch size. Thus, the breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents

What is claimed is:

1. A method of preparing microparticles having a selected microparticle polymer molecular weight, comprising:

(a) preparing a first phase, the first phase comprising a nucleophilic compound, a polymer having a starting molecular weight, and a solvent for the polymer;

(b) combining the first phase with a second phase under the influence of mixing means to form an emulsion;

(c) combining the emulsion and an extraction medium, thereby forming microparticles; and

(d) maintaining the first phase at a hold temperature for a hold period prior to step (b), the hold period of sufficient duration to allow the starting molecular weight of the polymer to reduce so that the selected microparticle polymer molecular weight is achieved.

2. The method of claim **1**, further comprising:

(e) increasing the hold temperature, thereby increasing molecular weight decay of the polymer to reduce a duration of the hold period.

3. The method of claim **1**, further comprising:

(e) decreasing the hold temperature, thereby decreasing molecular weight decay of the polymer to increase a duration of the hold period.

4. The method of claim **1**, wherein the starting molecular weight is in the range of from about 50 kD to about 250 kD.

5. The method of claim **1**, wherein the hold period is in the range of from about 0.05 hour to about 6 hours.

6. The method of claim **1**, wherein the hold temperature is in the range of from about 15° C. to about 35° C.

7. The method of claim **1**, wherein the mixing means is a static mixer.

8. The method of claim **1**, wherein the nucleophilic com pound is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

9. The method of claim **8**, wherein the solvent comprises benzyl alcohol and ethyl acetate.

10. The method of claim **1**, wherein the polymer is selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing.

11. The method of claim **10**, wherein the polymer is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 100:0 to about 50:50.

12. The method of claim **1**, further comprising:

(e) mixing the first phase during the hold period.

13. The method of claim **1**, wherein the selected microparticle polymer molecular weight is in the range of from about 10 kD to about 185.0 kD.

14. The method of claim **4**, wherein the selected microparticle polymer molecular weight is in the range of from about 10 kD to about 185.0 kD.

15. The method of claim **1**, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

16. The method of claim **4**, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

17. The method of claim 13, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

18. The method of claim 1, wherein the nucleophilic compound is an active agent.

19. The method of claim 1, wherein the nucleophilic compound is an inactive agent.

20. The method of claim 1, further comprising:

(e) adding an active agent to the first phase.

21. The method of claim 1, further comprising:

(e) adding an inactive agent to the first phase.

22. The method of claim 1, wherein the nucleophilic compound is basic.

23. The method of claim 1, wherein the nucleophilic compound is naltrexone.

24. The method of claim 1, wherein the nucleophilic compound is oxybutynin.

25. Microparticles having a selected microparticle polymer molecular weight prepared by the method of claim 1.

26. A method of preparing microparticles, comprising:

(a) providing a polymer having a starting molecular weight;

(b) dissolving the polymer and a nucleophilic compound in a solvent to form a first phase;

(c) combining the first phase with a second phase under the influence of mixing means to form an emulsion;

(d) combining the emulsion and an extraction medium, thereby forming microparticles; and

(e) maintaining the first phase at a hold temperature for a hold period prior to step (c), wherein the hold period is selected so that the starting molecular weight reduces so that a selected microparticle polymer molecular weight is achieved.

27. The method of claim 26, further comprising:

(f) increasing the hold temperature, thereby increasing molecular weight decay of the polymer to reduce a duration of the hold period.

28. The method of claim 26, further comprising:

(f) decreasing the hold temperature, thereby decreasing molecular weight decay of the polymer to increase a duration of the hold period.

29. The method of claim 26, wherein the starting molecular weight is in the range of from about 50 kD to about 250 kD.

30. The method of claim 26, wherein the hold period is in the range of from about 0.05 hour to about 6 hours.

31. The method of claim 26, wherein the hold temperature is in the range of from about 15° C. to about 35° C.

32. The method of claim 26, wherein the mixing means is a static mixer.

33. The method of claim 26, further comprising:

(f) adding an active agent to the first phase.

34. The method of claim 26, wherein the nucleophilic compound is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

35. The method of claim 34, wherein the solvent comprises benzyl alcohol and ethyl acetate.

36. The method of claim 26, wherein the polymer is selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing.

37. The method of claim 36, wherein the polymer is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 100:0 to about 50:50.

38. The method of claim 26, further comprising:

(f) mixing the first phase during the hold period.

39. The method of claim 26, wherein the selected microparticle polymer molecular weight is in the range of from about 10 kD to about 185.0 kD.

40. The method of claim 29, wherein the selected microparticle polymer molecular weight is in the range of from about 10 kD to about 185.0 kD.

41. The method of claim 29, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

42. The method of claim 26, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

43. The method of claim 39, wherein the starting molecular weight reduces by an amount in the range of from about 10% to about 50% to reach the selected microparticle polymer molecular weight.

44. The method of claim 26, wherein the nucleophilic compound is an active agent.

45. The method of claim 26, wherein the nucleophilic compound is an inactive agent.

46. The method of claim 26, further comprising:

(f) adding an inactive agent to the first phase.

47. The method of claim 26, wherein the nucleophilic compound is basic.

48. The method of claim 26, wherein the nucleophilic compound is naltrexone.

49. The method of claim 26, wherein the nucleophilic compound is oxybutynin.

50. Microparticles prepared by the method of claim 26.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,264,987 B1
DATED : July 24, 2001
INVENTOR(S) : Steven G. Wright et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,

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PATENT NO. : 6,264,987 B1
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Signed and Sealed this

Thirtieth Day of April, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US005702717A

United States Patent [19]

Cha et al.

[11] Patent Number: 5,702,717

[45] Date of Patent: Dec. 30, 1997

[54] **THERMOSENSITIVE BIODEGRADABLE POLYMERS BASED ON POLY(ETHER-ESTER)BLOCK COPOLYMERS**

[75] Inventors: **Younsik Cha**; **Young Kweon Choi**, both of Salt Lake City, Utah; **You Han Bae**, Kwangju, Rep. of Korea

[73] Assignee: **Macromed, Inc.**, Salt Lake City, Utah

[21] Appl. No.: **548,185**

[22] Filed: **Oct. 25, 1995**

[51] **Int. Cl.**[6] **A61K 9/10**; A61K 9/16

[52] **U.S. Cl.** **424/425**; 424/426; 424/424; 424/486; 424/501; 604/891.1

[58] **Field of Search** 424/424, 425, 424/426, 486, 501; 604/890.1, 891.1, 892.1

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Primary Examiner—Ralph H. Dean

Attorney, Agent, or Firm—Thorpe, North & Western, L.L.P.

[57] **ABSTRACT**

A system and method for the parenteral delivery of a drug in a biodegradable polymeric matrix to a warm blooded animal as a liquid with the resultant formation of a gel depot for the controlled release of the drug. The system comprises an injectable biodegradable block copolymeric drug delivery liquid having reverse thermal gelation properties. The delivery liquid is an aqueous solution having dissolved or dispersed therein an effective amount of a drug intimately contained in a biodegradable block copolymer matrix. The copolymer has a reverse gelation temperature below the body temperature of the animal to which it is administered and is made up of (i) a hydrophobic A polymer block comprising a member selected from the group consisting of poly(α-hydroxy acids) and poly(ethylene carbonates) and (ii) a hydrophilic B polymer block comprising a polyethylene glycol. Prior to use the liquid is maintained at a temperature below the reverse gelation temperature of the block copolymer. The liquid is parenterally administered into the animal by intramuscular, intraperitoneal, subcutaneous or similar injection with the liquid forming a gel depot of the drug and biodegradable block polymer as the temperature of the liquid is raised by the body temperature of the animal the reverse gelation temperature of the block copolymer. The drug is released at a controlled rate from the copolymer which biodegrades into non-toxic products. The degradation rate can be adjusted by proper selection of the poly(α-hydroxy acid) utilized in forming the biodegradable hydrophilic A block.

32 Claims, No Drawings

EXHIBIT B

THERMOSENSITIVE BIODEGRADABLE POLYMERS BASED ON POLY(ETHER-ESTER)BLOCK COPOLYMERS

The present invention relates to the preparation of thermosensitive biodegradable polymers and their use for parenteral administration of peptide and protein drugs. More particularly, this invention relates to thermosensitive biodegradable polymers containing peptide or protein drugs and to a process for preparing the same. This invention is made possible by the use of thermosensitive biodegradable polymers based on poly(ether-ester) block copolymers, which are described in detail hereinafter. The system is based the discovery that poly(ether-ester) block copolymers having certain molecular weight and composition ranges exist as a clear solution at, or about, ambient temperature in water but, when the temperature is raised to about body temperature, interact to form a semi-solid gel, emulsion or suspension.

BACKGROUND OF THE INVENTION AND SUMMARY OF PRIOR ART

Recently, many peptide/protein drugs, effective for a variety of therapeutic applications, have become commercially available through advances in recombinant DNA and other technologies. However, as polypeptides or proteins, their high molecular weight, degradation in the gastrointestinal tract, and short half-life in the body limits their routes of administration to intravenous or intramuscular and subcutaneous injection. And in many cases, daily injection is required for an extended period of time to get the expected therapeutic effect. Long term controlled delivery of such polypeptides or proteins is essential to provide for practical applications of these medications and to utilize these advances in biotechnology. Another problem is patient compliance. It is often difficult to get a patient to follow a prescribed dosage regimen, particularly when the prescription is for a chronic disorder and the drug has acute side-effects. Therefore, it would be highly desirable to provide a system for the delivery of drugs, and polypeptide and protein drugs in particular, at controlled rate over a specified period of time, without the above mentioned problems, in order to increase the therapeutic efficacy, the bioavailability and the patient compliance.

Drug-loaded polymeric devices are being investigated for long term, therapeutic treatment of different diseases. An important property of the polymeric device is biodegradability; meaning that the polymer can break down or degrade within the body to non-toxic components after all drug has been released. Furthermore, techniques, procedures, and solvents used to fabricate the device and load the drug should be safe for the patient, prevent irritation to surrounding tissue, and be a harmless medium for the peptide and protein drugs. Currently, biodegradable implantable controlled release devices are fabricated from crystalline polymers of polyglycolic or polylactic acids. Due to the hydrophobic properties of these polymers, drug loading and device fabrication using this material requires organic solvents such as methylene chloride, chloroform, acetic acid or dimethyl formamide. Obviously extensive drying is required after this process. In most cases, the final polymeric device is fabricated in a distinct solid shape (sphere, slab or rod) requiring surgical implantation, and resulting in tissue irritation.

Currently, there are not many synthetic or natural polymeric materials which can be used for the controlled delivery of peptide and protein drugs because of the strict regulatory compliance requirements, such as biocompatibility, clear degradation pathway and safety of degradation products. The most widely investigated and advanced biodegradable polymers in regard to available toxicological and clinical data are the aliphatic poly(α-hydroxy acids), such as poly(d,l- or l-lactic acid) (PLA) and poly(glycolic acid) (PGA) and their copolymers. These polymers are commercially available and are presently being used as bioerodable sutures in surgery. The first FDA-approved system for controlled release of peptides, the Lupron Depot™, is also based on lactic acid-glycolic acid copolymers. The Lupron Depot™ consists of injectable microcapsules, which release leuprolide acetate over a prolonged period (e.g., about 30 days) for the treatment of prostate cancer. Based on this history of use, lactic acid-glycolic acid copolymers have been the materials of choice in the initial design of parenteral sustained release delivery systems using a biodegradable carrier.

However, even though there has been some limited success, these polymers also have problems associated with their physicochemical properties and methods of fabrication. Hydrophilic macromolecules, such as polypeptides, cannot diffuse out through the hydrophobic matrix or membrane of polylactides. Drug loading and device fabrication using polylactide requires organic solvents and the solid dosage form may induce tissue irritation.

A. S. Sawhney and J. A. Hubbell, *J. Biomed. Mat. Res.*, 24, 1197–1411 (1990), synthesized terpolymers of d,l-lactide, glycolide and ε-caprolactone which degrade rapidly in vitro. For example, a terpolymer composition of 60% glycolide, 30% lactide, and 10% ε-caprolactone exhibited a half-life of 17 days. The hydrophilicity of the material was increased by copolymerization with a polyether surfactant prepolymer (Pluronic F-68). This prepolymer is a block copolymer comprising about 80% w. of a hydrophobic poly(propylene oxide) block and 20% w. of a hydrophilic poly(ethylene oxide) block. Copolymerization with the surfactant prepolymer resulted in a stronger and partly crystalline material which was mechanically stable at physiological temperature (e.g. ≈37° C.) in water. The half-life of this copolymer was slightly increased compared to the base polymer. However, it is known that Pluronic type of polymeric surfactants, particularly the poly(propylene oxide) block portions, are not biodegradable.

Other implantable delivery systems, such as shown in Dunn et al, U.S. Pat. Nos. 4,938,763 and 5,278,202, have also been known for some time. One unique aspect of such formulations is the fact that, when formulated, they maintain a liquid consistency which allows injection using 22/23 gauge needle. These polymers are either thermoplastic or thermosetting. The thermoplastic system involves the forming of a polymeric solution in a suitable solvent. When the polymeric solution is injected into the body and is exposed to body fluids or water, the solvent diffuses away from the polymer-drug mixture and water diffuses into the mixture where it coagulates the polymer encapsulating the drug within the polymeric matrix as the implant solidifies. The thermoplastic solution requires the use of an organic solvent such as N-methyl-2-pyrrolidone, methyl ethyl ketone, dimethylformamide, propylene glycol, THF, DMSO, dodecylazacycloheptan-2-one (Azone) and the like. The thermosetting system comprises the synthesis of crosslinkable polymers which can be formed and cured in-situ through the use of a curing agent. The polymers are first formed using a polyol initiator and catalyst to form polyol-terminated prepolymers which are further converted to acrylic ester-terminated prepolymers. Just prior to injection,

the acrylic prepolymer solution has added thereto a curing agent such as benzoyl peroxide or azobisisobutyronitrile. Once injected, the crosslinking reaction proceeds until sufficient molecular weight has been obtained to cause the polymer to solidify. These polymers are formed primarily by the polymerization or copolymerization of biodegradable hydrophobic polylactides, polyglycolides, polycaprolactones and the like. The polymer type used has degradation times in the range of weeks to months. The degradation rate can be adjusted by choosing the appropriate polymer. The polymers are non-toxic and are well tolerated by the body and the system is easy to formulate. These polymer formulations provide a novel approach for a biodegradable implant since they can be easily injected, avoiding the use of surgical procedures. Their biocompatibility and biodegradability is also well established. The gel matrix once formed will release the drug in a controlled manner and then degrade to products which are easily metabolized and excreted. These thermosetting and thermoplastic formulations incorporate the advantages of an implant while circumventing the need for surgery prior to administration or after the release is complete. However, the major drawback of the thermoplastic formulations is the use of organic solvents which can be toxic or irritating to the body tissues. The thermosetting system requires that the drug be admixed with the prepolymer solution prior to additions of the catalysts because the curing reaction is quite rapid and injection must take place almost immediately following the addition of the curing agent.

An optimum material for use as an injectable or implantable polymeric drug delivery device should be biodegradable, be compatible with hydrophilic or hydrophobic drugs, and allow fabrication with simple, safe solvents, such as water and not require additional polymerization or reaction following administration.

One system, which can be fabricated in aqueous solution, is a class of block copolymers composed of two different polymer blocks, i.e. hydrophilic poly(ethylene oxide) blocks and hydrophobic poly(propylene oxide) blocks. These are synthesized to make up a triblock of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) and marketed under the Pluronic™ or Poloxamer™ tradenames. The triblock copolymers absorb water to form gels which have potential for use in topical pharmaceutical and cosmetic systems, i.e. in topical drug delivery systems. These are surface-active block copolymers which exhibit reverse thermal gelation behavior and possess drug release characteristics. However, the Pluronic system is non-biodegradable and its gel properties and drug release kinetics are in need of substantial improvement.

The Pluronic™, Poloxamer™ type triblock copolymers undergo solidification or gelation as the temperature of the solution is raised above a critical temperature (gelation temperature). These polymers form micelles (microscopic spheres incorporating water) at low concentration and turn into thick, continuous gels at high concentrations and elevated temperature (≈30° C.).

As shown in Table 1, the Pluronic-6™ series, including Pluronic F-68™, form a gel at a minimum concentration of 50–60% (w/w) at room temperature, Pluronic F-88™ forms a gel at 40% at 25° C., and Pluronic F-108™ forms a gel at 30% concentration. The thermal gelation mechanism can be explained by micellar desolvation and swelling to form a pseudo-cross-linking among the polymer micelles. The mechanism of gelation involves the incorporation of polymer molecules into micelles as a function of temperature. As the micelle size increases with temperature, the micelles may undergo a thermally induced swelling (micellar enlargement) together with a desolvation of the inner polymer core. This swelling has been associated with conformational changes in the methyl groups of the polyoxypropylene chain. This phenomena is enhanced by hydrophobic polymer interactions at higher temperatures, resulting in a physically entangled, stable network. The network between the polymer molecules produces a progressive increase of the viscosity and the consistency of the vehicle upon heating.

TABLE 1

Physicochemical characteristics and gel-forming property of selected Pluronics ™

	F-68	F-88	F-98	F-108	F-127
Molecular weight	8350	10800	13500	15500	11500
PEO:PPO wt. ratio	80:20	80:20	80:20	80:20	70:30
PPO weight	1750	2250	2750	3250	3850
Melting point (°C.)	50	55	56	57	56
Conc (%) and Temp (°C.)					
20% at 25°C.	−	−	−	−	+
20% at 37°C.	−	−	+	+	+
30% at 25°C.	−	−	+	+	+
30% at 37°C.	−	+	+	+	+
40% at 25°C.	−	+	+	+	+
40% at 37°C.	+	+	+	+	+

PEO: poly(ethylene oxide)
PPO: poly(propylene oxide)
=: no gel-formation
+: gel-formation

Pluronic F-127™ (Poloxamer 407™) is one of the least toxic of the block copolymers and forms a gel at only 20% concentration in water, at 20° C. Pluronic F-127™ consists by weight of approximately 70% ethylene oxide and 30% propylene oxide with an average molecular weight of 11500. The unique characteristics of this polymer is reverse thermal gelation; concentrated solutions (20–30 wt/wt %) of the copolymer are fluid at low temperature (under 10° C.), but are soft gel at body temperature.

Potentially, protein drugs could be loaded into these types of gels simply by increasing the temperature of an aqueous solution of protein and polymer, thereby trapping and incorporating the protein with the gel network. Since the solvent is water, the bioactivity of the protein should be preserved and the release rate of the protein from the gel could be controlled.

Several studies have been done on the usefulness of Pluronic F-127™ gels as an injectable, sustained release depot. Toxicological evaluation of Pluronic™ vehicles following intramuscular (i.m.) injections in rabbits has been reported, T. P. Johnson et al., J. Parenteral Sci. & Tech., Vol. 39, No. 2, pp 83–88 (1985). Sustained release of urease from a Poloxamer™ gel matrix has also been reported, T. P. Johnson et al., J. Parenteral Sci. a Tech., Vol. 44, No. 2, pp 58–65 (1990). The sustained delivery of IL-2 from a Poloxamer 407™ gel matrix following intraperitoneal (i.p.) injection in mice is reported in T. P. Johnson et al., Pharmaceutical Research, Vol. 9, No. 3, pp. 425–434 (1992). Subcutaneous (s.c.) injection of IL-2 in 30% (w/w) Pluronic F-127™ enhanced antitumor immune responses by sustained IL-2 activity at the tumor sites as reported by K. Morikawa et al. Cancer Research, 47, 37–41 (1987). An alteration of the rat kidney to efficiently clear inulin by means of glomerular filtration was observed after i.m. injection of inulin-Pluronic™ gel formulations was described by K. F. Fults et al., J. Parental Sci. & Tech., Vol. 43, No. 6, 279–285 (1989).

There is a strong need for hydrophilic biodegradable materials which can be used to incorporate water-soluble polypeptide drugs in solution. A. S. Sawhney et al., Macromolecules, Vol 26, No. 4, 581–589 (1993) synthesized macromers having a poly(ethylene glycol) central block, extended with oligomers of α-hydroxy acids such as oligo (d,l-lactic acid) or oligo(glycolic acid) and terminated with acrylate groups. Using non-toxic photoinitiators, the macromers can be rapidly polymerized with visible light. Due to the multifunctionality of the macromers, polymerization results in the formation of crosslinked gels. The gels degrade upon hydrolysis of the oligo(α-hydroxy acid) regions into poly(ethylene glycol), the α-hydroxy acid, and oligo(acrylic acid) and their degradation rates can be tailored by appropriate choice of the oligo(α-hydroxy acid) from less than 1 day to up to 4 months. However, in this system, a photoinitiator, an additional component, is employed as well as an additional process such as photocrosslinking.

Okada et al., Japanese Patent 2-78629 (1990), synthesized biodegradable block copolymeric materials by transesterification of poly(lactic acid) (PLA) or poly(lactic acid)/glycolic acid (PLA/GA) and poly(ethylene glycol) (PEG). The molecular weight range for PLA/GA was 400 to 5,000 and for PEG, 200 to 2,000. The mixture was heated at 100° to 250° C. for 1 to 20 hours under a nitrogen atmosphere. The product was miscible with water and formed a hydrogel. It also precipitated in water above room temperature depending on the composition. In other words, it is possible to change the water-solubility and hydrophobicity by exposing the polymer solution to elevated temperatures. The molecular structure of the product obtained cannot be defined based on the description given. However, the typical experimental conditions were: 30 g of poly(d,l-lactic acid) (MW 1590) was mixed with 20 g PEG (MW 570–630) and heated in a molten state without the use of any solvent at 250° C. under nitrogen for 4.5 hours. The resulting product was immediately dissolved by dispersing it in 300 ml ice-water. A white polymer precipitate was obtained by heating the dispersion to 50° C. The polymer was purified by repeating this process and dried at 50° C. under vacuum to obtain a semi-waxy material. The materials can be mixed with various peptide and protein solutions and used as an injectable sustained release formulation. It can also be freeze-dried to make a solid block, or vacuum dried to make a paste, which can be implanted. It can also be used as a mixture with other biocompatible materials or microporous materials such as hydroxyapatite.

T. Matsuda, ASAIO Journal, M512–M517 (1993) used a biodegradable polymeric gel to deliver a potent peptidyl antiproliferative agent, angiopeptin, to prevent the myointimal hyperplasia that occurs when a diseased vessel is replaced with an artificial graft or treated by an intravascular device. A highly viscous liquid of a block copolymer composed of poly(lactic acid) and poly(ethylene glycol) (PLA-PEG) block segments was used as an in situ coatable drug carrier. The materials were supplied by Taki Chemical Co., Ltd., Hyogo, Japan. A prolonged slow release of angiopeptin from the polymer gel, consisting of 0.5 g PLA-PEG and 0.5 mg angiopeptin, was observed in vitro over a few weeks when the gel was kept in a buffer solution maintained at 37° C. No early burst release of angiopeptin was observed. Based on these results, the local sustained angiopeptin release from the biodegradable polymeric gel coated on an injured vessel in vivo was theorized to be effective.

L. Martini et al., J. Chem. Soc., Faraday Trans., 90(13), 1961–1966 (1994) synthesized very low molecular weight ABA type triblock copolymers by incorporating hydrophobic poly(ε-caprolactone) which is known to be subject to degradation in vivo by hydrolytic chain scission involving the ester linkages and reported the solution properties of the PCL-PEG-PCL block copolymers. Clouding was observed visually when an aqueous solution of the block copolymers were slowly heated. The cloud points of 2 wt % aqueous solutions of the copolymers were 65° C. and 55° C. for PCL-PEG-PCL (450:4000:450) and PCL-PEG-PCL (680:4000:680) respectively. Reversible gelation on cooling solutions of PCL-PEG-PCL (680:4000:680) was observed at critical concentrations and temperatures ranging from 13% at 25° C. to 30% at 80° C. No lower gel-sol transition was observed on further cooling the solutions to 0° C. The gelation of a micellar solution of a triblock copolymer of caprolactone and oxyethylene, as with that of micellar solutions Of oxyethylene/oxypropylene and oxyethylene/oxybutylene copolymers, is almost an athermal process. The in vitro degradation rate of PCL-PEG-PCL (680:4000:680) was very slow. Only ca. 20% decrease in molar mass (from GPC) was observed over a period of 16 weeks.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide block copolymer drug delivery systems that are biodegradable, exhibit reverse thermal gelation behavior and possess good drug release characteristics.

It is also an object of this invention to provide methods to fabricate copolymeric biodegradable thermosensitive peptide or other drug delivery devices.

A still further object of this invention is to provide a drug delivery system for the parenteral administration of hydrophilic drugs and particularly highly water-soluble peptide and protein drugs.

Yet another object of this invention is to provide a method for the parenteral administration of drugs in a biodegradable polymeric matrix resulting in the formation of a gel depot within the body from which the drugs are released at a controlled rate with the corresponding biodegradation of the polymeric matrix.

These and other objects will become apparent from the following summary and detailed description of the various embodiments making up this invention.

As used herein the following terms shall have the assigned meanings:

"Parenteral" shall mean any route of administration other than the alimentary canal and shall specifically include intramuscular, intraperitoneal, intra-abdominal, subcutaneous, and, to the extent feasible, intravenous.

"Solution", "aqueous solution" and the like, when used in reference to a combination of drug and biodegradable block copolymer contained in such solution, shall mean a water based solution having such drug/polymer combination dissolved or uniformly suspended therein at a functional concentration and maintained at a temperature below the LCST of the block copolymer.

"Drug delivery liquid" or "drug delivery liquid having reverse thermal gelation properties" shall means a "solution" suitable for injection into a warm-blooded animal which forms a depot upon having the temperature raised above the LCST of the copolymer.

"Depot" means a drug delivery liquid following injection into a warm-blooded animal which has formed a gel upon the temperature being raised to or above the LCST.

"LCST, or lower critical solution temperature", means the temperature at which the biodegradable block copolymer

undergoes reverse thermal gelation, i.e. the temperature below which the copolymer is soluble in water and above which the block copolymer undergoes phase separation to form a semi-solid containing the drug and the block copolymer.

The terms "LCST", "gelation temperature" and "reverse thermal gelation temperature" or the like shall be used interchangeably in referring to the LCST.

"Gel", when used in reference to a semi-solid combination of drug and biodegradable block copolymer at a temperature at or above the LCST, shall be inclusive of such combinations in the form of gels, emulsions, dispersions, suspensions and the like.

"Biodegradable" meaning that the block polymer can break down or degrade within the body to non-toxic components after all drug has been released.

"Drug" shall mean any organic compound or substance having bioactivity and adapted or used for a therapeutic purpose.

"Peptide", "polypeptide", "oligopeptide" and "protein" shall be used interchangeably when referring to peptide or protein drugs and shall not be limited as to any particular molecular weight, peptide sequence or length, field of bioactivity or therapeutic use unless specifically stated.

"Poly(α-hydroxy acid)" shall mean a poly(α-hydroxy acid) polymer per se or a poly(α-hydroxy acid) polymer or copolymer derived from the ring opening polymerization of an α-hydroxy acid precursor, such as a corresponding lactide, glycolide or lactone.

Basic to the present invention is the utilization of a block copolymer having hydrophobic or "A" block segments and hydrophilic or "B" block segments. Generally the block copolymer will be a triblock copolymer, i.e. an ABA or BAB type block copolymer. However, the block copolymer could also be a multiblock copolymer having repeating BA or AB units to make $A(BA)_n$ or $B(AB)_n$ copolymers where n is an integer or from 2 to 5.

The biodegradable hydrophobic, or A block, segment is preferably a poly(α-hydroxy acid) member derived or selected from the group consisting of poly(d,l-lactide), poly (l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ε-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ε-caprolactone co-lactic acid), poly(ε-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid and bi- or terpolymers thereof. The above listing is not intended to be all inclusive or necessarily self limiting as combinations or mixtures of the various α-hydroxy acids can be used to form homopolymeric or copolymeric hydrophobic block segments and still be within the scope of the invention. The average molecular weight of such α-hydroxy acid polymeric blocks is between about 500 and 10,000 and is more preferably between about 500 and 3,000.

Another biodegradable hydrophobic or A block segment can be a low molecular weight enzymatically degradable poly(ethylene carbonate). The average molecular weight of such poly(ethylene carbonate) polymeric blocks is between about 200 and 10,000 and is more preferably between about 200 and 3,000.

The hydrophilic B block segment is preferably polyethylene glycol (PEG) having an average molecular weight of between about 1000 to 20,000 and is more preferably between about 1,000 and 5,000.

Both ABA and BABtype hydrophilic/hydrophobic block copolymers synthesized as disclosed herein possess reverse thermal gelation properties and are biodegradable. BAB type block copolymers possess similarities to the Pluronic system described above, but are quite different in that the hydrophobic poly(α-hydroxy acid) or poly(ethylene carbonate) A block is biodegradable and more biocompatible than the hydrophobic PPO block of the Pluronic system.

As noted, the B block is formed from various, but appropriate, molecular weights of hydrophilic poly(ethylene glycol) (PEG). PEG was chosen as the hydrophilic water-soluble block domain because of its unique biocompatibility, nontoxicity, micelle forming properties, and rapid clearance from the body.

The hydrophobic A blocks are synthesized and utilized because of their biodegradable and biocompatible properties. The in vitro and in vivo degradation of these hydrophobic polymer blocks is well understood and the degradation products are natural metabolites that are readily eliminated by the body.

The molecular weight of the hydrophobic poly(α-hydroxy acid) or poly(ethylene carbonate) A blocks, relative to that of the water-soluble B PEG block, is regulated to be sufficiently small to retain desirable water-solubility and gelling properties. Also, the proportionate weight ratios of hydrophilic B block to the hydrophobic A block must also be sufficient to enable the block copolymer to possess water solubility at temperatures below the LCST (lower critical solution temperature). Generally, the PEG block should be at least 50% w. of the block copolymer to remain water-soluble and is perferably higher. Thus, biodegradable block copolymers possessing thermally reversible gelation properties are prepared wherein the hydrophilic B block makes up about 50 to 85% by weight of the copolymer and the hydrophobic A blocks makes up about 15 to 50% by weight of the copolymer.

The concentration at which the block copolymers are soluble at temperatures below the LCST may be considered as the functional concentration. Generally speaking, block copolymer concentrations of up to about 50% by weight can be used and still be functional. However, concentrations in the range of about 3 to 40% are preferred and concentrations in the range of about 10–25% be weight are most preferred. In order to obtain a viable phase transition of the polymer, a certain minimum concentration is required. At the lower functional concentration ranges the phase transition may result in the formation of an emulsion rather than a gel. At higher concentrations, a gel network is formed. The actual concentration at which an emulsion may phase into a gel network may vary according to the ratio of hydrophobic A block to hydrophilic B block and the composition and molecular weights of each of the blocks. Since both emulsions and gels can both be functional it is not imperative that the acutal physical state be precisely determined. However, the formation of a swollen gel network is preferred.

The mixture of the biodegradable polymer and peptide/protein drugs may be prepared as an aqueous solution at a lower temperature than the gelation temperature of the polymeric material. Once injected into the body via intramuscular, subcutaneous or intraperitoneal route as a liquid, the drug/polymer formulation will undergo a phase change and will preferably form a highly swollen gel, since body temperature will be above the gelation temperature of the material.

This system will cause minimal toxicity and mechanical irritation to the surrounding tissue due to the biocompatibility of the materials and will be completely biodegradable within a specific predetermined time interval. Once gelled,

the drug release from the polymeric matrix can be controlled by proper formulation of the various copolymer blocks.

In both of the ABA and BAB copolymer embodiments, a solution of the drug and polymer is prepared and then implanted into the body as a solution which gels or solidifies into a depot as the temperature is raised due to the reverse gelation properties of the drug/polymer composition. It may also be desirable to formulate these compositions for oral use in the form of tablets or capsules.

This may be accomplished by the preparation of microspheres containing peptide or protein drugs by using either the ABA type or BAB type thermosensitive biodegradable block copolymers described above. The thermosensitive polymer solution in cold water is mixed with aqueous solution of peptide/protein drugs and is then added dropwise into a warm oil. The raising of the temperature causes the gelation of the polymer and the drug is entrapped into the solidifying or partially precipitating gel droplets suspended in the warm oil. The solidified droplets become partially hardened microspheres which can then be separated, washed, and dried under vacuum. The resultant microspheres can be loaded into capsules or compressed into tablets to make a sustained release oral dosage form for peptide/protein drugs. The drug loaded microspheres will disintegrate slowly especially at body temperature which is above the gelling point of the polymer.

The only limitation as to how much drug can be loaded onto the copolymer is one of functionality. Generally speaking, the drug can make up between about 0.1 to 10% by weight of the drug polymer combination with ranges of between about 1 to 5% being preferred.

This invention is applicable to polypeptides quite generally, but is most useful for polypeptides which are relatively stable at temperatures of up to about 50° C.

Many labile peptide and protein drugs can be subjected to the reverse thermal gelation encapsulation process described herein.

While not being specifically limited to the following, pharmaceutically useful polypeptides may be selected from group consisting of oxytocin, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinising hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α,β,γ (IFN-α,β,γ), gastrin, tetragastrin, pentagastrin, urogastroine, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), renin, bradykinin, bacitracins, polymixins, colistins, tyrocidin, gramicidines, and synthetic analogues, modifications and pharmacologically active fragments thereof, monoclonal antibodies and soluble vaccines.

The only limitation to the peptide or protein drug which may be utilized is one of functionality.

In some instances, the functionality or physical stability of proteins can also be increased by various additives to aqueous solutions of the peptide or protein drugs. Additives, such as polyols (including sugars), amino acids, proteins such as collagen and gelatin and certain salts may be used. These additives can readily be incorporated into the reverse thermal gelation process of the present invention.

Developments in protein engineering may provide the possibility of increasing the inherent stability of peptide or proteins also. While such resultant engineered or modified proteins may be regarded as new entities in regards to regulatory implications, that does not alter their suitability for use in the present invention. One of the typical examples of modification is PEGylation of polypeptides. The stability of the polypeptide drugs can be significantly improved by covalently conjugating water-soluble polymers such as polyethylene glycol with the polypeptide. Another example is the modification of the aminoacid sequence in terms of the identity or location of one or more residues by terminal and internal addition and deletion or substitution (e.g., deletion of cysteine residues or replacement by alanine or serine).

Any improvement in stability enables a therapeutically effective polypeptide or protein to be continuously released over a prolonged period of time following a single administration of the pharmaceutical composition to a patient.

In addition to peptide or protein based drugs, other drugs, at similar concentratons, may be utilized such as anticancer agents, antibiotics, antiinflammatory agents, hormones, and the like. Typical anticancer agents include adriamycin, mitomycin, bleomycin, cisplatin, carboplatin, doxorubicin, daunorubicin, 5-fluorouracil, methotrexate, taxol, taxotere, actinomycin D and the like.

If desired, the degradation rate of the block copolymer may be modified as desired to release the drug over a predetermined time period. This may be accomplished by the introduction of a bi- or terpolymer structure into the hydrophobic segment.

Different poly(α-hydroxy acids) degrade at different rates. For example, the hydrophobic poly(ε-caprolactone) segment in the block copolymer degrades very slowly. The primary hydrolyric degradation product of poly(ε-caprolactone) is 6-hydroxyhexanoic acid. Studies with tritium labeled poly (ε-caprolactone) showed that about 70% of the excreted radioactivity is in the form of tritiated water which indicates a substantial metabolism of 6-hydroxyhexanoic acid. The metabolic pathway for 6-hydroxyhexanoic acid can be deduced from the metabolic pathways established for hexanoic acid and adipic acid. 6-Hydroxyhexanoic acid is mainly transformed to adipic acid by ω-oxidation in the microsomes of liver and kidney. The adipic acid is then metabolized by β-oxidation in much the same fashion as fatty acids yielding predominantly carbon dioxide and water.

Based on the above, one would expect that the hydrophobic poly(ε-caprolactone) segment in a PCL-PEG-PCL block copolymer to degrade very slowly. For optimal use in a polymeric drug delivery system, it is desirable to see no polymeric materials are left over after the complete depletion of the drug from the polymer. The degradation rate of the PCL-PEG-PCL block copolymer system can be further modified by incorporating a bi- or terpolymer structure into the hydrophobic PCL segment. For example, incorporation of glycolide and/or lactide units to the PCL segment to form a bi- or terpolymeric poly(α-hydroxy acid) segment will significantly accelerate the degradation rate of this hydrophobic block copolymer segment.

Other bi- or terpolymeric hydrophobic combinations using different poly(α-hydroxy acids) can be utilized to derive block segments having desired degradation rates.

Another adaptation in the preparation of thermosensitive drug delivery systems is to utilize the interaction between peptide/protein drugs in contact with these temperature sensitive biodegradable gels. Usually the duration of sustained release from a thermosensitive gel device is not very long. For example, about 8 hours of sustained release was observed after subcutaneous injection of the non-degradable

Pluronic F-127™ (PEO-PPO-PEO) gel preparations. The interaction between the peptide/protein drugs and the temperature sensitive biodegradable gels will affect physical/chemical compatibility and bioactivity of the drugs. For example, in the PCL-PEG-PCL or PLA-PEG-PLA type systems, the hydrophobic interaction between the drug and polymer can extend the duration of drug release. Also, the nature of the drug/polymer complexes will change the release kinetics and release duration of the controlled release system. For example, it is known that salt formation between a carboxy terminated polyester and a peptide/protein drug can change the physico-chemical properties of the complex such as its solubility in organic solvents.

It is also possible to modify polymeric system by the incorporation of ionic groups to cause ionic interactions between the drug and polymer to adjust the drug release profile. For example, carboxyl functional groups can be incorporated into the hydrophobic segment of the thermosensitive polymer system by employing malic acid or its derivatives as a comonomer during the synthesis. Other polycarboxylic acids could also be utilized. Thus the acidic group can interact with basic group of peptide/protein drugs. It is also known that the covalent attachment of the hydrophilic polyethylene glycol segment to the protein will increase the stability of the drug in solution and prevent aggregation. It is also known that certain surfactants significantly increase protein stability. The modified hydrophilic-hydrophobic block copolymer which contains ionic groups such as carboxy group therefore serve, not only as a release rate modifier, but also as a stabilizing agent for the labile protein because of the specific drug-polymer interaction.

Another embodiment or approach to the obtaining of thermosensitive polymers having a desired rated of degradation is to incorporate an enzymatically degradable hydrophobic segment in the block copolymer system described in the present invention. This approach has a significant meaning because of the fact that the poly(ether-ester) block copolymer system is hydrolyrically labile and difficult to store for lengthy periods of time in an aqueous environment. It would be desirable to provide a hydrophobic polymeric material which is stable in an aqueous environment in vitro but readily degrades by enzymatic action in vivo. Poly (ethylene carbonate) is one of the best candidate polymers for this purpose. This polymer is flexible at room temperature due to its low glass transition temperature (Tg, 6° C.) and is very hydrophobic. No degradation occurs in water at room temperature i.e. about 37° C. However, a slow decrease of molecular weight is observed when the polymer is treated with a boiling dilute HCl solution. On the other hand, rapid degradation occurred when the polymer is implanted in the animal body. A thick slab (about 300 μm thickness) of a poly(ethylene carbonate) polymer completely disappeared within 2–3 weeks after implantation as noted by T. Kawaguchi et al., *Chem. Pharm. Bull.* 31 (4) 1400 (1983). Surprisingly, no enzymatic degradation occurs at all in the case of poly(propylene carbonate) despite the structural similarity. The rate of enzymatic degradation can be controlled by blending or copolymerization of the poly (ethylene carbonate) and poly(propylene carbonate). When the poly(ethylene carbonate) is hydrolyzed, both ends are terminated with hydroxy group. Various chemical reactions such as isocyanate, acid chloride, N-hydroxy succinimide reactions can be utilized to synthesize ABA or BAB type block or multiblock copolymers described in the present invention.

The synthesized polymers will be characterized for molecular weight, block length, polymer composition, critical micelle concentration, surface activity, gelation temperature, water content of gels, tissue compatibility, and biodegradability of the polymers.

The reverse thermal self-gelling systems described herein are very useful as a vehicle with which to increase the viscosity of a protein formulation and thus, sustain the rate of release of a protein into the systemic circulation following extravascular administration. These polymers will be especially useful for incorporating peptide and protein drugs into polymeric carriers because proteins are sensitive to heat, organic solvents, and changes in pH and ionic strength, and are thus prone to loss in their biological activity. Therefore, a sustained release dosage form can be prepared with these polymers, in which a drug is dissolved (or dispersed) in a cold polymer solution, forming a drug-entrapped semi-solid gel immediately after injection into the body. The polymer/drug mixture can be injected at any site of the body via intramuscular, subcutaneous, or intraperitoneal route. The drug/protein release rates and duration will be a function of solidified gel density, molecular weight of the drug/protein, and other factors such as hydrophobic or ionic interactions. Bulk degradation will occur because the injected gel is hydrophilic and water is present in the bulk of the gel. The polymer will be degraded into small fragments that may or may not be water-soluble. The water-soluble oligomers will be excreted directly or through various metabolic pathways. The water-insoluble oligomers will be taken up by macrophages and foreign body giant cells and further degraded in the lysosomes.

Because of the surfactant-like properties of these block copolymer systems, the diluted polymer solution forms a milky emulsion when the polymers loses its solubility in water. This self-emulsifying system is also of great interest because moderately hydrophobic drugs can be dissolved by the surface active triblock copolymers disclosed herein and then can be incorporated into emulsions (or suspensions) formed spontaneously at body temperature. The triblock copolymers can also be considered as degradable nonionic surfactants which are superior in function to the non-degradable Pluronic™ system. Certain peptides and proteins will also be adsorbed onto or entrapped into this system and formulated as a new type of controlled release delivery system. The drugs can be released slowly with degradation of the particles. Eventually, no further microencapsulating process, which are time-consuming and mostly requires organic solvents, is needed. The poly(ether-ester) block copolymers described in the present invention has temperature-sensitivity and has great potential for the development of the self-gelling or self-emulsifying, biodegradable depot system which can be injected extravascularly and release the incorporated or entrapped drug in a sustained manner.

As noted above, the biodegradable poly(ether-ester) block copolymers which the desirable thermally reversible gelation properties are those wherein the hydrophilic B block preferably makes up about 50 to 85% by weight of the copolymer and the hydrophobic A blocks makes up about 15 to 50% by weight of the copolymer. Also, the functional concentration at which these block copolymers are soluble at temperatures below their LCST may be considered may vary. When use for purposes of injection the block copolymer concentration may be as high as about 50% by weight with the only limitation be that of functionality. Taking into consideration the above discussions relative to the formation of emulsions and gels, concentrations in the range of about 3 to 40% are preferred and concentrations in the range of about 10–25% be weight are most preferred. The phase

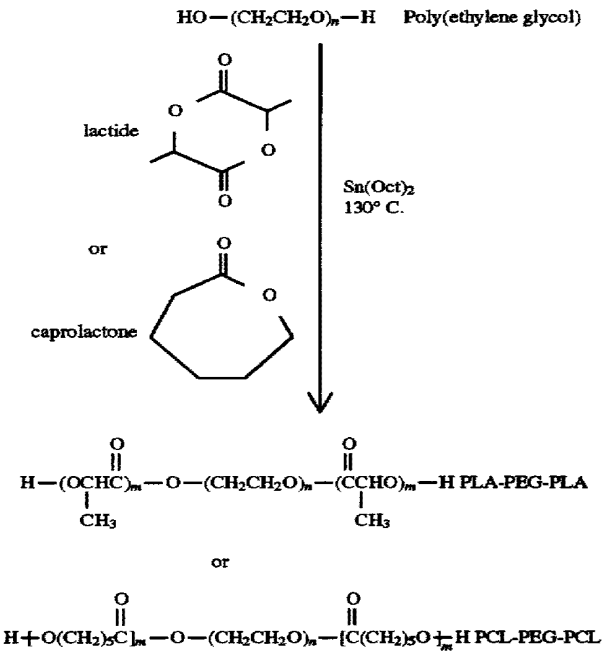
transition of the drug/copolymer combination above the LCST is the critical parameter required. Within the guidelines stated herein, one skilled in the art can determine, without undue experimation, the appropriate drug loading, polymer composition and concentration, degradation rates, degree of gelation/emulsion formation, etc.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

In order to illustrate preferred embodiments of this invention, schemes for synthesizing copolymers consisting of hydrophobic (A) and hydrophilic (B) blocks of the ABA type are illustrated. In both Schemes 1 and 2 the hydrophilic B block can be prepared using various molecular weights of poly(ethylene glycol) (PEG).

In Scheme 1, the preparation of a series of triblock copolymers is illustrated. Either a polylactide (PLA) or poly(ϵ-caprolactone)(PCL) can be prepared in a melt process by ring opening polymerization of lactide and ϵ-caprolactone initiated by reaction with PEG as follows:

Scheme 1



In a typical experiment, 3 g of lactide (or caprolactone) and stannous octoate (0.1 wt/wt % to monomer) is added into a reactor equipped with a high-vacuum valve containing an appropriate amount of PEG under dry nitrogen, and the reactor is tightly closed after evacuation. Polymerization is carried out at 130° C. for 30 hours. After cooling to room temperature, the reaction mixture is dissolved in methylene chloride followed by precipitation in an excess amount of diethyl ether. The product is dried under vacuum to a constant weight. The obtained copolymer are subjected to characterization using 1H-NMR (Bruker AS 200 FT spectrometer) and gel permeation chromatography using Ultrastyragel columns (Waters) calibrated with polystyrene standards. The overall molecular weights and compositions are determined by 1H-NMR. Properties of ABA block copolymers obtained by this process are shown in Table 2. The compositions for the copolymers were almost close to the values expected from the feed condition, indicating that polymerization was quantitative. The narrow, unimodal GPC traces demonstrated that no homopolymer was produced and that no side reaction such as chain scission and transesterification occurred.

TABLE 2

Results of bulk polymerization of lactide and caprolactone initiated by poly(ethylene glycol) at 130°C.

Code	feed (PEG wt/wt %)	Copolymer Composition Calculated	Copolymer Composition Experimental*
PECL-1	50	500-1000-500	480-1000-480
PELA-1	77	500-3400-500	510-3400-510
PELA-2	63	1000-3400-1000	1080-3400-1080
PELA-3	53	1500-3400-1500	1530-3400-1530

*calculated from 1H-NMR spectra
PECL: PCL-PEG-PCL triblock copolymer
PELA: PLA-PEG-PLA triblock copolymers

All block copolymers shown in Table 2 were soluble in water at low temperature and showed solidification (thermosensitivity) as the temperature was elevated sufficiently. In all cases, the phase transition occurred instantly within a narrow temperature range. The transition temperatures of 5 wt/wt % aqueous solutions are presented in Table 3.

TABLE 3

Thermal transition temperatures of the various poly(ether-ester)block copolymer aqueous solutions (5 wt/wt %)

Code	PEG content (wt/wt %)	Transition temperature (°C.)
PECL-1	50	10
PELA-1	77	50
PELA-2	63	40
PELA-3	53	30

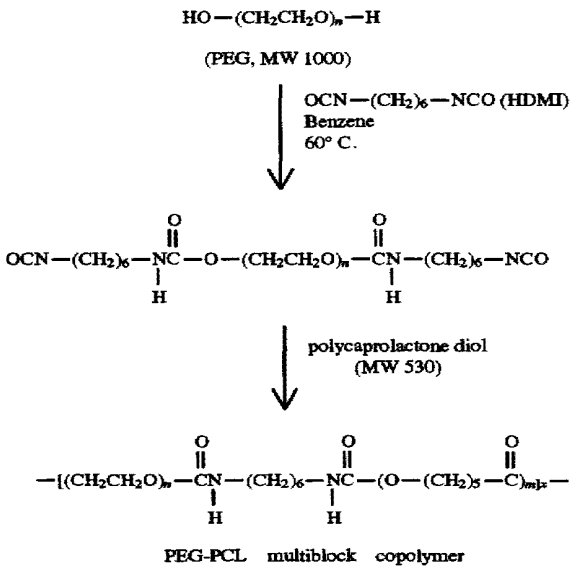
PECL: PCL-PEG-PCL triblock copolymer
PELA: PLA-PEG-PLA triblock copolymers

This kind of physical phenomenon is similar to the temperature-sensitivity found in surface-active block copolymers of poly(ethylene oxide)-poly(propylene oxide) (Pluronics™ or Poloxamer™) which are referenced above.

The system described herein shows both reverse thermal gelation and self-emulsification depending on polymer structure. A PCL-PEG multiblock copolymer formed according to Scheme 2, illustrated below, formed a semi-solid gel matrix on heating, while PCL-PEG-PCL triblock copolymer (PECL-1 shown in Table 2) formed an emulsion. These two different responses on thermal change are basically the same in regards to mechanism, and result from difference in concentration, temperature and polymer structure.

In Scheme 2, the preparation of a multiblock PEG-PCL copolymer is illustrated. A PEG polymer (MW≈1000) is reacted with an excess amount-of hexamethylene diisocyanate (HMDI) in benzene at 60° C. to obtain an isocyanate (—N=C=O) group terminated PEG prepolymer. The PEG prepolymer is then further chain extended with a bifunctional polycaprolactone diol (MW≈530). The resulting product is a polyethylene glycol-polycaprolactone (PEG-PCL) multiblock copolymer with the blocks being connected by means of an urethane linkage. The reaction scheme is as follows:

Scheme 2



PEG-PCL multiblock copolymer

EXAMPLE 1

Synthesis of PECL-1

A mixture of 3 g of ϵ-caprolactone and stannous octoate (0.1 wt/wt % to monomer) was added into a reactor equipped with a high-vacuum valve containing an appropriate amount of PEG under dry nitrogen, and the reactor was tightly closed after evacuation. Polymerization was carried out at 130° C. for 30 hours. After cooling to room temperature, the reaction mixture was dissolved in methylene chloride followed by precipitation in an excess amount of diethyl ether. The product was dried under vacuum to a constant weight.

EXAMPLE 2

Synthesis of PELA-1,2,3.

A mixture of 3 g of lactide and stannous octoate (0.1 wt/wt % to monomer) was added into a reactor equipped with a high-vacuum valve containing an appropriate amount of PEG under dry nitrogen, and the reactor was tightly closed after evacuation. Polymerization was carried out at 130° C. for 30 hours. After cooling to room temperature, the reaction mixture was dissolved in methylene chloride followed by precipitation in an excess amount of diethyl ether. The product was dried under vacuum to a constant weight.

EXAMPLE 3

Poly(d,l-lactic acid) (MW≈2,500) (PLA) was synthesized by the conventional condensation polymerization of d, l-lactic acid at elevated temperature under reduced pressure. To the melt of this poly(d,l-lactic acid) was added polyethylene glycol (MW≈6,000) (PEG). The mixture was heated at 180° C. for 20 hours under a reduced pressure of about 50 mm Hg. with continuous bubbling of dry nitrogen gas to form a PLA-PEG-PLA block copolymer (average MW≈2500:6000:2500).

A one gram sample of the triblock copolymer was placed in a glass vial and 10 ml of ice-cold water was added. The polymer dissolved to yield a tan-colored liquid. The solution was heated to 37° C. in a water bath and was solidified to a non-flowing gel. After storing in a refrigerator for several hours, the gel again became a fluid, i.e. the polymer underwent reversible sol-gel transition. On heating the solution to 60° C., the polymer separated from the aqueous phase and formed as an opaque precipitate. On cooling in an ice water bath, the opaque precipitate became a transparent tan weight.

The above suggests that the PLA-PEG-PLA polymer is soluble in water at temperatures below the LCST, e.g., about 0° C., forms a gel when raised above the LCST, e.g., about 37° C., but collapses to form a precipitate when heated to about 60° C. The precipitate formed at 60° is sparingly soluble, or is at least slow to bring into solution, when cooled below the LCST. Such polymers, even though not completely soluble in cold solutions, may still be effective networks for injection or implantation into the body for the delivery of drugs as shown in Example 4.

EXAMPLE 4

To 0.2 g of the tan colored semi-solid gel obtained in Example 3 is mixed 0.1 ml of concentrated human calcitonin solution (10 mg/ml) by gentle blending with a spatula. The mixture is put into 10 mls of phosphate buffered saline (PBS) at 37° C. Fine polymeric calcitonin containing particles, having a diameter of between about 5 to 20 μm, are formed from the surface of the gel and slowly dispersed into the buffer to form a milky suspension of drug polymer microspheres.

The dilution of the polymeric gel and calcitonin blend in PBS formed a microsphere suspension that, when formulated under aseptic conditions, can be directly injected or implanted into the body.

When placed in the body, the calcitonin will be released slowly from the polymeric gel and diffuse out to the surrounding area and the polymer, being biodegradable, will be eliminated from the body.

EXAMPLE 5

Malic acid is polymerized with d,l-lactic acid to form a carboxyl group-containing oligomeric polyester (MW≈3,000). To a melt of this carboxylated copolymer is added polyethylene glycol (MW 5,000) which is predried under high vacuum at an elevated temperature and then further heated at 180° C. under a nitrogen atmosphere for 15 hours.

EXAMPLE 6

The block copolymer formed in Example 5 is dissolved in ice cold water and mixed with a solution of basic, heat stable platelet-derived growth factor (PDGF-B, isoelectric point 10.2). The mixture is injected to the mixing head of a T. K. Homomixer Mark II which is rotating at 10,000 rpm in a buffer solution at 500° C. The drug is incorporated into the copolymer by an simultaneous dispersion and precipitation process. The leaching of the drug during this process is reduced by the ionic interaction and complex formation between the carboxylated copolymer and the drug. The precipitated drug containing copolymer particles are collected and freeze dried.

EXAMPLE 7

An aliphatic poly(ethylene carbonate) polymer was synthesized by methods known in the art as follows. Carbon dioxide was reacted with ethylene oxide at 60° C. in a pressurized bomb reactor in the presence of diethyl zinc-water catalyst. The resulting polymer was purified by being

dissolved in methylene chloride and reprecipitated in methanol. The purified high molecular weight poly(ethylene carbonate) (PEC) (average MW≈100,000) was refluxed in 1% HCl solution to obtain a low molecular weight poly (ethylene carbonate) (MW≈2,000) having hydroxyl groups at both ends of the polymer chain, e.g. a bifunctional diol.

Separately, polyethylene glycol (average MW≈3,400) was reacted with an excess amount of hexamethylene diisocyanate (HMDI) in benzene at 60° C. to obtain isocyanate (—N=C=O) group terminated prepolymer. The prepolymer was further chain extended with the bifunctional poly (ethylene carbonate) diol as prepared above. The resulting product was a polyethylene glycol-polyethylene carbonate (PEG-PEC) multiblock copolymer with the blocks being connected by means of an urethane linkage.

EXAMPLE 8

The multiblock copolymer synthesized in Example 7 is dissolved in ice cold water. Zinc insulin (PENTEX recombinant human insulin, zinc salt, is added to the PEG-PEC multiblock copolymer solution and gently mixed until a clear solution is obtained. The polymer/insulin salt solution is dropped into a buffered solution, pH of about 5.5 and at a temperature above the LCST (lower critical solution temperature) of the multiblock copolymer. Solidified multiblock copolymer/insulin beads are formed, collected by filtration and freeze dried.

Because of the hydrolyrically stable, but enzymatically degradable nature of the PEC block segment, the insulin release profile is different from the conventional hydrolyrically unstable block copolymers and the duration of insulin release is more extended.

EXAMPLE 9

Methoxy polyethylene glycol chloroformate (average MW≈2,000) is reacted with poly(ethylene carbonate) diol (MW≈2,000) obtained in Example 7 to form a BAB type block copolymer having PEG endblocks and possessing reversible thermal gelation properties. This block copolymer is enzymatically degradable due to the hydrophobic PEC central block segment.

The resulting polymer is dissolved in ice cold water and mixed with interleukin-2(IL-2) solution. Because of the marked hydrophobicity of the IL-2 protein, it can be stabilized by the hydrophobic interaction with the surfactant-like copolymer. The IL-2 polymer can be stored as an aqueous solution for extended periods of time due to the enzymatically degradable, but hydrolyrically stable nature of the copolymer. After gelling at body temperature, a much longer duration of drug release can be expected as compared to the non-degradable Pluronic™ or Poloxamer™ systems described in the prior art.

The above description will enable one skilled in the art to make and use drug loaded block copolymers based on reverse thermal gelation properties. The description is not intended to be an exhaustive statement of specific peptides, or other drugs which can be utilized and loaded onto the biodegradable block or multiblock copolymers. Neither are all block copolymers which may be prepared specifically shown. It will be apparent to one skilled in the art that various modifications may be made without departing from the scope of the inventions which is limited only by the following claims and their functional equivalents.

We claim:

1. An injectable biodegadable block copolymeric drug delivery liquid having reverse thermal gelation properties comprising an aqueous solution having uniformly contained therein between about 3 and 40% by weight of

(a) an effective amount of a drug intimately contained in

(b) a biodegradable block copolymer comprising

(I) less than 50% by weight of a hydrophobic A polymer block comprising a member selected from the group consisting of poly(α-hydroxy acids) and poly(ethylene carbonates) and

(ii) more than 50% by weight of a hydrophilic B polymer block comprising a polyethylene glycol; and

wherein said liquid is maintained at a temperature below the lower critical solution temperature of said block copolymer.

2. An injectable drug delivery liquid according to claim **1** wherein said hydrophilic polyethylene glycol polymer block of said block copolymer has an average molecular weight of between 1000 and 20,000.

3. An injectable drug delivery liquid according to claim **2** wherein said hydrophilic polyethylene glycol polymer block comprises up to 85% by weight of said block copolymer and said hydrophobic A polymer block comprises at least 15% by weight of said block copolymer.

4. An injectable drug delivery liquid according to claim **3** wherein said hydrophobic A polymer block is a poly(α-hydroxy acid).

5. An injectable drug delivery liquid according to claim **4** wherein said poly(α-hydroxy acid) is a member derived or selected from the group consisting of poly(d,l-lactide), poly (l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ε-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ε-caprolactone-co-lactic acid), poly(ε-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid and bi- or terpolymers thereof.

6. An injectable drug delivery liquid according to claim **5** wherein said poly(α-hydroxy acid) polymer block has an average molecular weight of between about 500 and 10,000.

7. An injectable drug delivery liquid according to claim **6** wherein said hydrophobic poly(α-hydroxy acid) polymer A block has an average molecular weight of between about 500 and 3,000 and said hydrophilic polyethylene glycol polymer B block has an average molecular weight of between about 1,000 and 5,000.

8. An injectable drug delivery liquid according to claim **6** wherein said block copolymer is a triblock copolymer having a configuration selected from the group consisting of ABA and BAB block segments.

9. An injectable drug delivery liquid according to claim **8** wherein the hydrophobic A block segment contains a poly (α-hydroxy acid) selected from the group consisting of poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), and poly (l-lactide-co-glycolide).

10. An injectable drug delivery liquid according to claim **8** wherein the hydrophobic A block segment contains a poly(α-hydroxy acid) consisting of poly(ε-caprolactone).

11. An injectable drug delivery liquid according to claim **3** wherein said hydrophobic polymer A block is a poly (ethylene carbonate) having an average molecular weight of between about 200 and 10,000.

12. An injectable drug delivery liquid according to claim **11** wherein said hydrophobic poly(ethylene carbonate) polymer A block has an average molecular weight of between about 200 and 3,000 and said hydrophilic polyethylene glycol polymer B block has an average molecular weight of between about 1,000 and 5,000.

13. An injectable drug delivery liquid according to claim **8** or **11** wherein said drug is a polypeptide.

14. An injectable drug delivery liquid according to claim 13 wherein said polypeptide is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinising hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α,β,γ (IFN-α,β,γ), gastrin, tetragastrin, pentagastrin, urogastroine, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), renin, bradykinin, bacitracins, polymixins, colistins, tyrocidin, gramicidines, and synthetic analogues, modifications and pharmacologically active fragments thereof, monoclonal antibodies and soluble vaccines.

15. An injectable drug delivery liquid according to claim 8 or 11 wherein said drug is an anti-cancer agent.

16. An injectable drug delivery liquid according to claim 15 wherein said anti-cancer agent is a member selected from the group consisting of adriamycin, mitomycin, bleomycin, cisplatin, carboplatin, doxorubicin, daunorubicin, 5-fluorouracil, methotrexate, taxol, taxotere, and actinomycin D.

17. A method for the parenteral delivery of a drug in a biodegradable polymeric matrix to a warm blooded animal as a liquid with the resultant formation of a gel depot for the controlled release of said drug, which comprises;

(1) providing an injectable biodegradable block copolymeric drug delivery liquid having reverse thermal gelation properties comprising an aqueous solution having uniformly contained therein between about 3 and 40% by weight of
  (a) an effective amount of a drug intimately contained in
  (b) a biodegradable block copolymer having a LCST below the body temperature of said warm blooded animal and comprising
    (i) less than 50% by weight of a hydrophobic A polymer block comprising a member selected from the group consisting of poly(α-hydroxy acids) and poly(ethylene carbonates) and
    (ii) more than 50% by weight of a hydrophilic B polymer block comprising a polyethylene glycol;

(2) *maintaining* said liquid a temperature below the LCST of said block copolymer; and

(3) injecting said liquid parenterally into said warm blooded animal forming a gel depot of said drug and biodegradable block polymer as the temperature of the liquid is raised by the body temperature of said animal to be above the LCST of said polymer.

18. A method according to claim 17 wherein said hydrophilic polyethylene glycol polymer block of said block copolymer has an average molecular weight of between 1000 and 20,000.

19. A method according to claim 18 wherein said hydrophilic polyethylene glycol polymer block comprises up to 85% by weight of said block copolymer and said hydrophobic A polymer block comprises at least 15% by weight of said block copolymer.

20. A method according to claim 19 wherein said hydrophobic A polymer block is a poly(α-hydroxy acid).

21. A method according to claim 20 wherein said poly (α-hydroxy acid) is a member derived or selected from the group consisting of poly(d,l-lactide), poly(l-lactide), poly(d,l-lactide-co-glycolide), poly(l-lactide-co-glycolide), poly(ε-caprolactone), poly(γ-butyrolactone), poly(δ-valerolactone), poly(ε-caprolactone-co-lactic acid), poly(ε-caprolactone-co-glycolic acid-co-lactic acid), hydroxybutyric acid, malic acid and bi- or terpolymers thereof.

22. A method according to claim 21 wherein said poly (α-hydroxy acid) polymer block has an average molecular weight of between about 500 and 10,000.

23. A method according to claim 22 wherein said hydrophobic poly(α-hydroxy acid) polymer A block has an average molecular weight of between about 500 and 3,000 and said hydrophilic polyethylene glycol polymer B block has an average molecular weight of between about 1,000 and 5,000.

24. A method according to claim 22 wherein said block copolymer is a triblock copolymer having a configuration selected from the group consisting of ABA and BAB block segments.

25. A method according to claim 24 wherein the hydrophobic A block segment contains a poly(α-hydroxy acid) selected from the group consisting of poly(d,l-lactide), poly (l-lactide), poly(d,l-lactide-co-glycolide), and poly(l-lactide-co-glycolide).

26. A method according to claim 24 wherein the hydrophobic A block segment contains a poly (α-hydroxy acid) consisting of poly (ε-caprolactone).

27. A method according to claim 19 wherein said hydrophobic polymer A block is a poly(ethylene carbonate) having an average molecular weight of between about 200 and 10,000.

28. A method according to claim 27 wherein said hydrophobic poly(ethylene carbonate) polymer A block has an average molecular weight of between about 200 and 3,000 and said hydrophilic polyethylene glycol polymer B block has an average molecular weight of between about 1,000 and 5,000.

29. A method according to claim 24 or 25 wherein said drug is a polypeptide.

30. A method according to claim 29 wherein said polypeptide is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinising hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α,β,γ (IFN-α,β,γ), gastrin, tetragastrin, pentagastrin, urogastroine, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), renin, bradykinin, bacitracins, polymixins, colistins, tyrocidin, gramicidines, and synthetic analogues, modifications and pharmacologically active fragments thereof, monoclonal antibodies and soluble vaccines.

31. A method according to claim 24 or 25 wherein said drug is an anti-cancer agent.

32. A method according to claim 31 wherein said anti-cancer agent is a member selected from the group consisting of adriamycin, mitomycin, bleomycin, cisplatin, carboplatin, doxorubicin, daunorubicin, 5-fluorouracil, methotrexate, taxol, taxotere, and actinomycin D.

* * * * *

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United States Patent [19]

Rathi et al.

[11] Patent Number: 6,004,573

[45] Date of Patent: Dec. 21, 1999

[54] **BIODEGRADABLE LOW MOLECULAR WEIGHT TRIBLOCK POLY(LACTIDE-CO-GLYCOLIDE) POLYETHYLENE GLYCOL COPOLYMERS HAVING REVERSE THERMAL GELATION PROPERTIES**

[75] Inventors: **Ramesh C. Rathi**; **Gaylen M. Zentner**, both of Salt Lake City, Utah

[73] Assignee: **MacroMed, Inc.**, Salt Lake City, Utah

[21] Appl. No.: **08/943,167**

[22] Filed: **Oct. 3, 1997**

[51] **Int. Cl.**[6] **A61F 2/02**; A61F 2/14; A61F 6/06; A61K 9/48

[52] **U.S. Cl.** **424/426**; 424/428; 424/430; 424/434; 424/435; 424/436; 424/437; 424/443; 424/449; 424/451; 424/464

[58] **Field of Search** 424/426, 428, 424/430, 434, 435, 436, 437, 443, 449, 451, 464

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(List continued on next page.)

Primary Examiner—Carlos Azpuru

Attorney, Agent, or Firm—Thorpe, North & Western, LLP

[57] **ABSTRACT**

A water soluble biodegradable ABA-type block copolymer made up of a major amount of hydrophobic poly(lactide-co-glycolide) copolymer A-blocks and a minor amount of a hydrophilic polyethylene glycol polymer B-block, having an overall average molecular weight of between about 3100 and 4500, possesses reverse thermal gelation properties. Effective concentrations of the block copolymer and a drug may be uniformly contained in an aqueous phase to form a drug delivery composition. At temperatures below the gelation temperature of the copolymer the composition is a liquid and at temperatures at or above the gelation temperature the composition is a gel or semi-solid. The gelation temperature is preferably at or below body temperature of a warm-blooded animal. The composition may be administered to a warm-blooded animal as a liquid by parenteral, ocular, topical, transdermal, vaginal, transurethral, rectal, nasal, oral, or aural delivery means and is a gel at body temperature. The composition may also be administered as a gel. The drug is released at a controlled rate from the gel which biodegrades into non-toxic products. The release rate of the drug may be adjusted by changing various parameters such as hydrophobic/hydrophilic component content, copolymer concentration, molecular weight and polydispersity of the block copolymer. Because the copolymer is amphiphilic it functions to increase the solubility and/or stability of drugs in the composition.

24 Claims, 6 Drawing Sheets

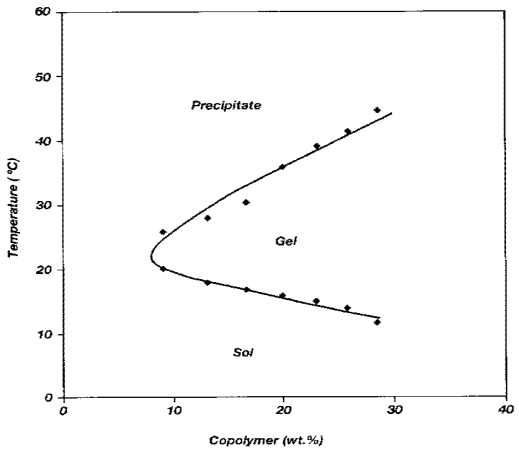


EXHIBIT C

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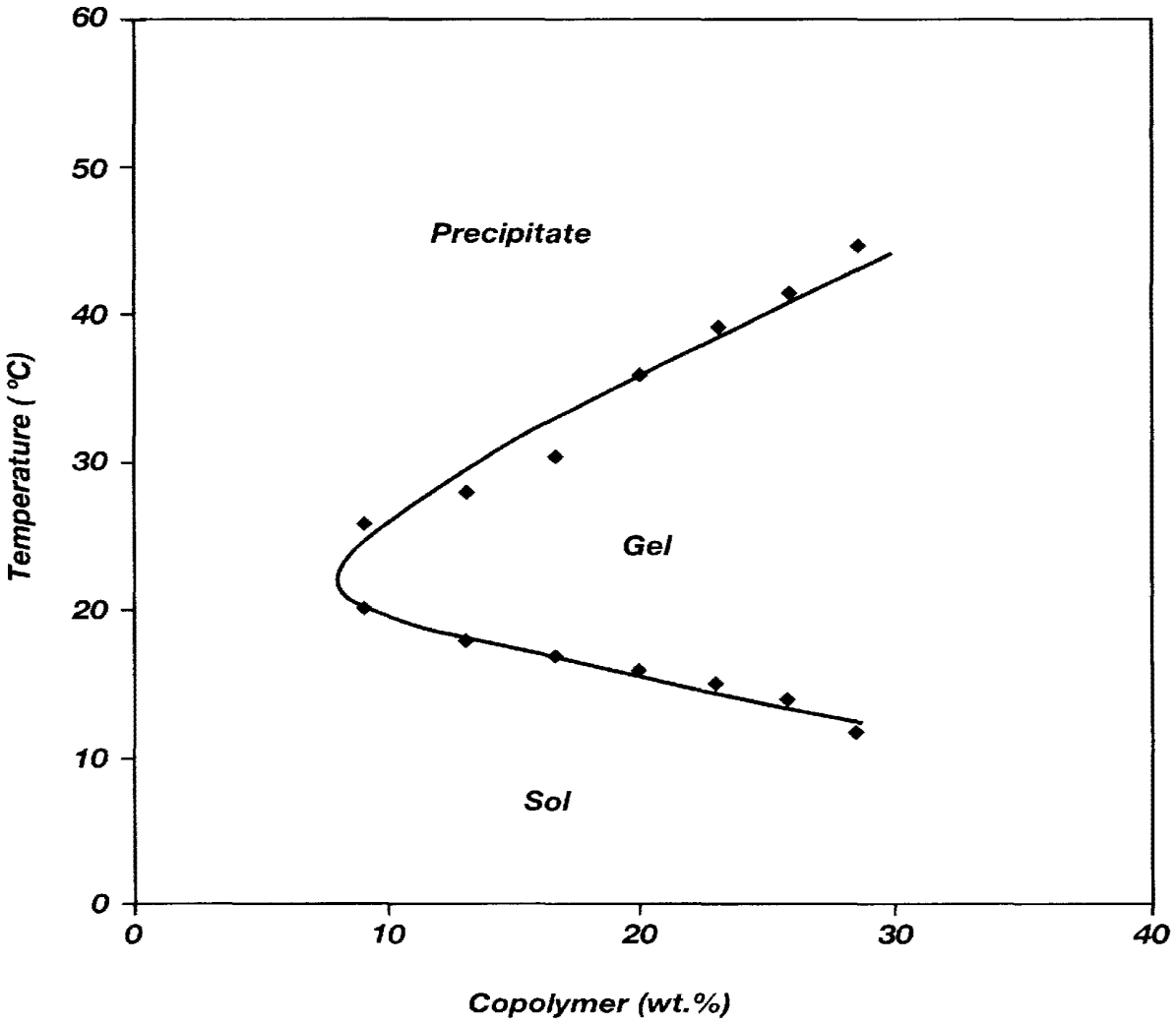

60
50
40
30
20
10
0
Temperature (°C)
Precipitate
Gel
Sol
0
10
20
30
40
Copolymer (wt.%)

Fig. 1

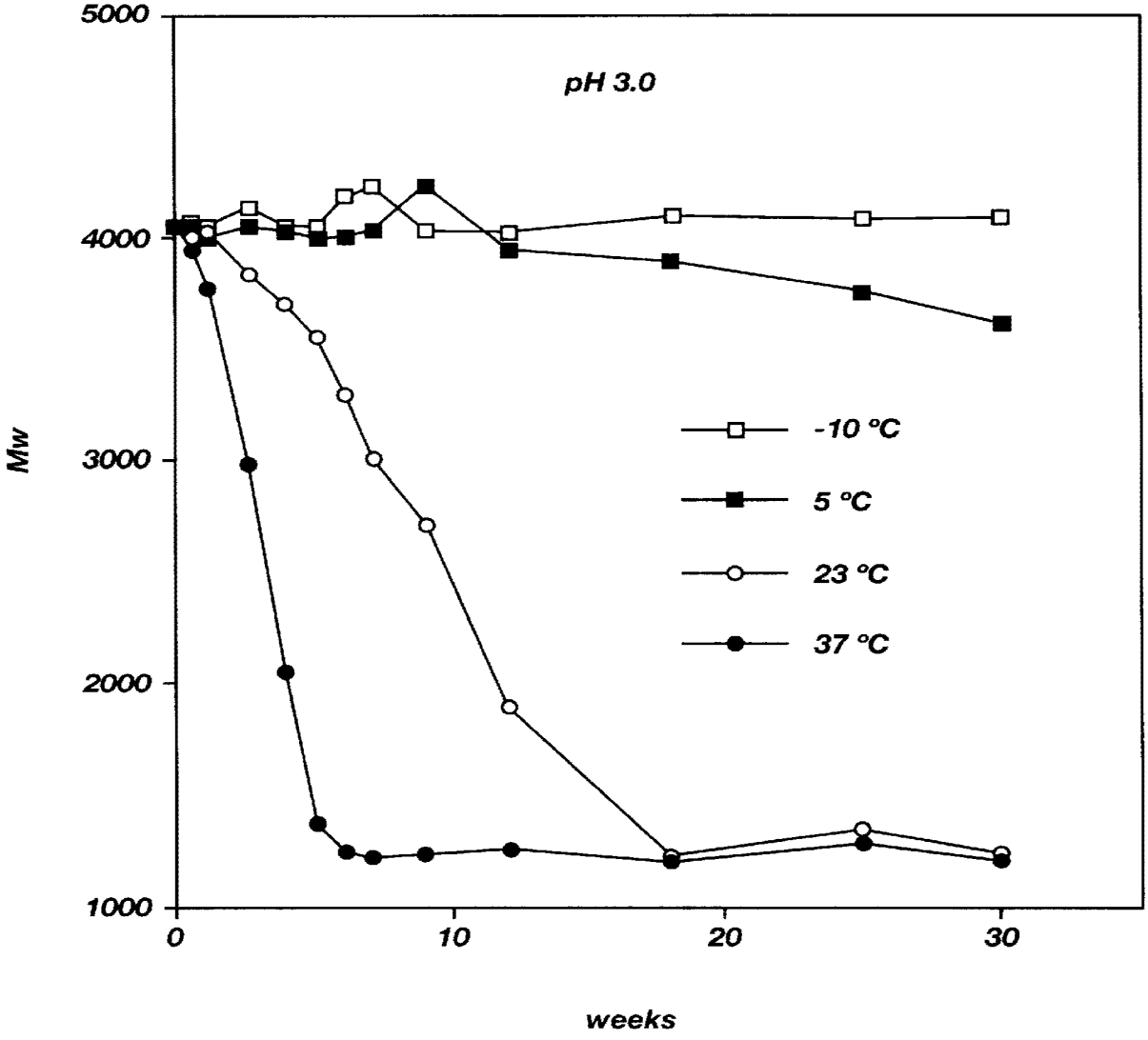


Fig. 2a

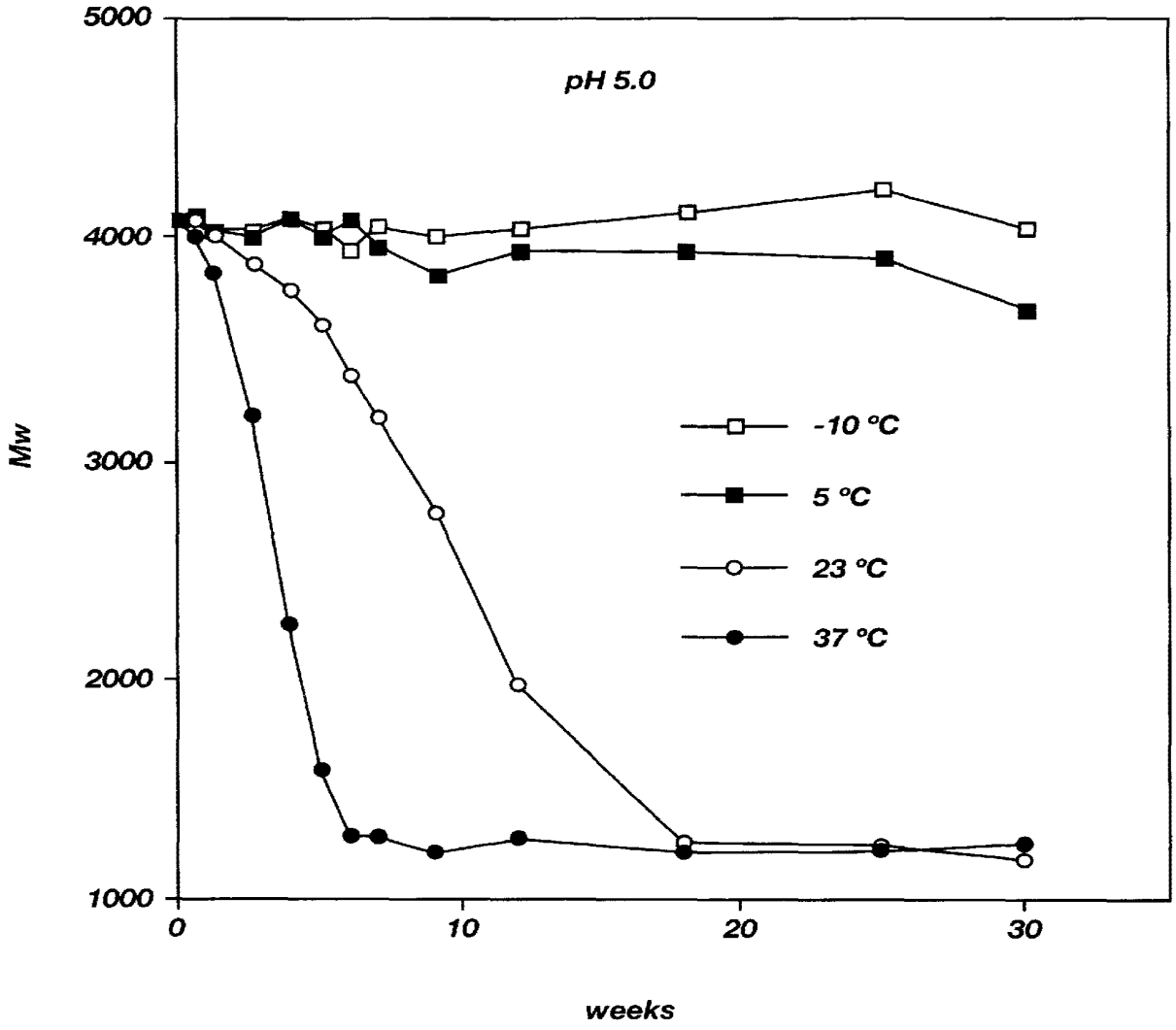


Fig. 2b

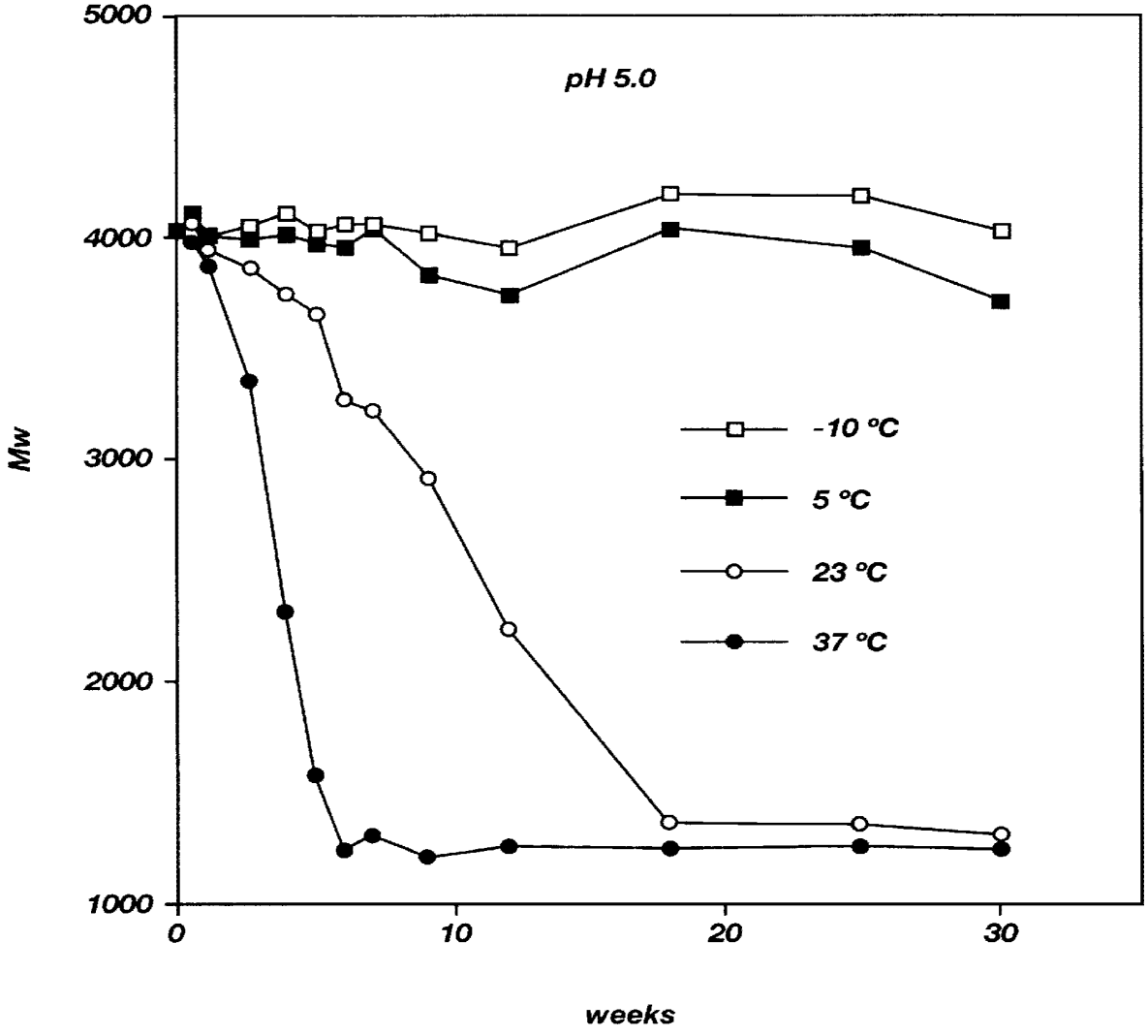


Fig. 2c

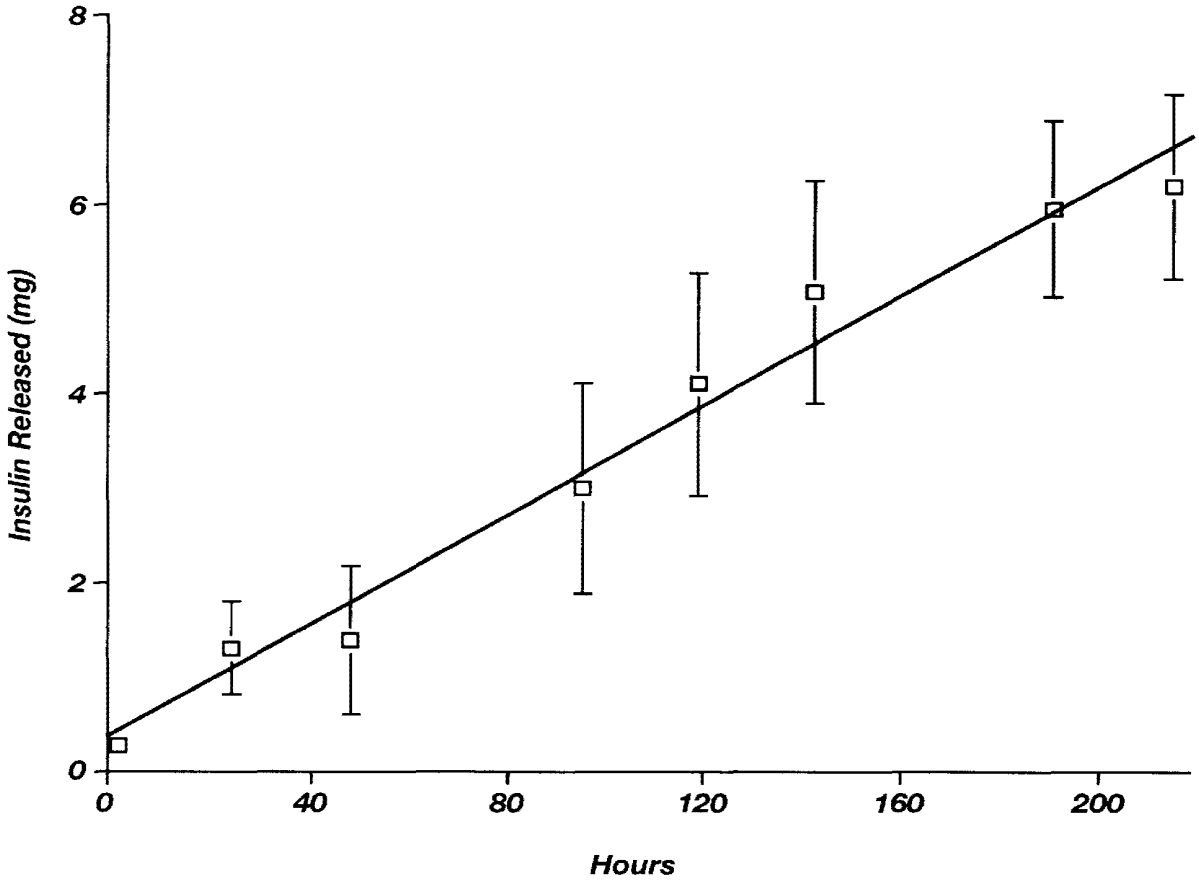


Fig. 3

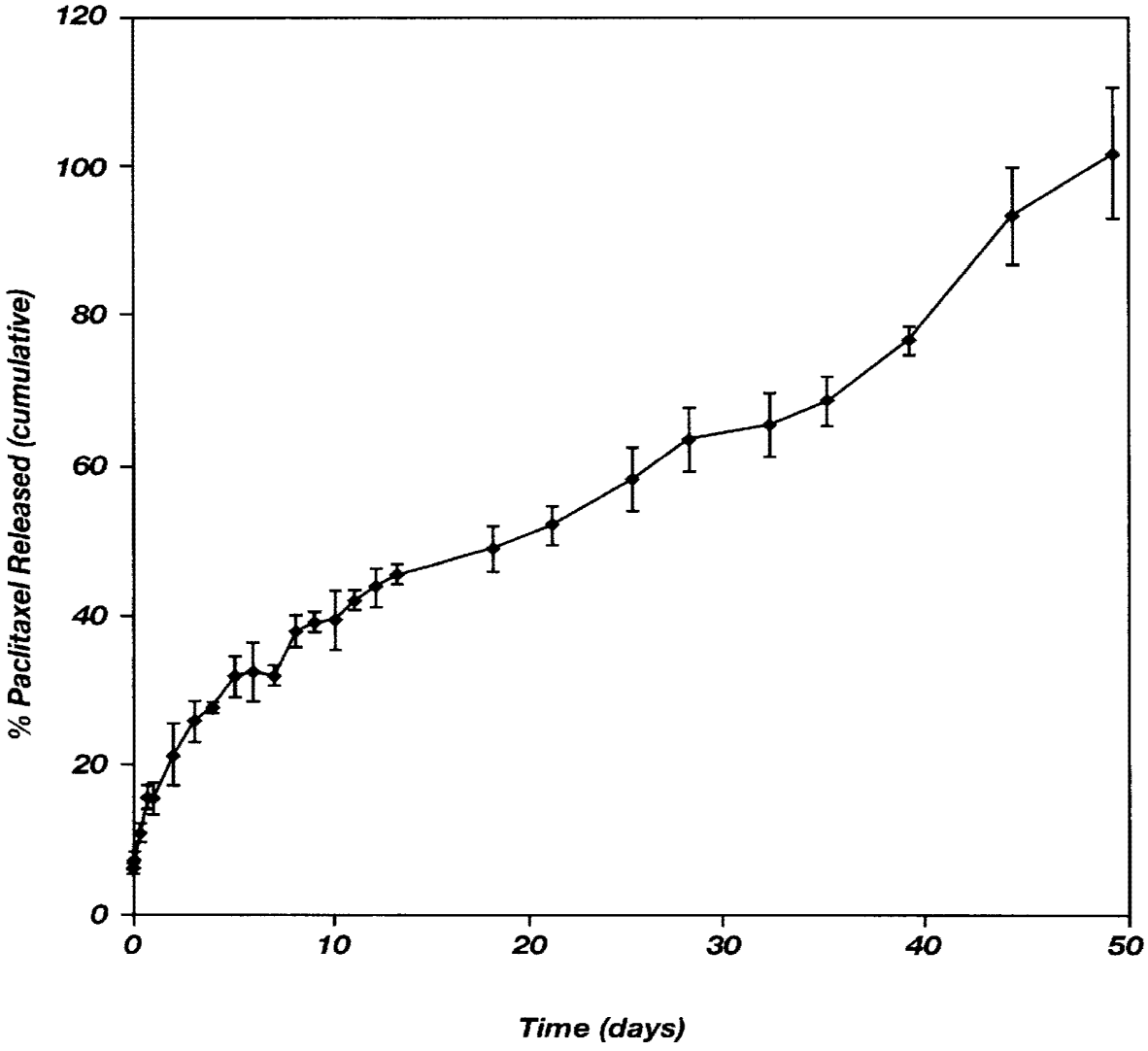

120
100
80
60
40
20
0
% Paclitaxel Released (cumulative)
0
10
20
30
40
50
Time (days)

Fig. 4

BIODEGRADABLE LOW MOLECULAR WEIGHT TRIBLOCK POLY(LACTIDE-CO-GLYCOLIDE) POLYETHYLENE GLYCOL COPOLYMERS HAVING REVERSE THERMAL GELATION PROPERTIES

The present invention relates to water soluble, low molecular weight, thermosensitive, biodegradable block copolymers having a high weight percentage of hydrophobic block(s), and their use for parenteral, ocular, topical, transdermal, vaginal, transurethral, rectal, nasal, oral, or aural administration of drugs. This invention is made possible by the use of thermosensitive biodegradable triblock copolymers based on poly(lactide-co-glycolide) and polyethylene glycol blocks, which are described in detail hereinafter. The system is based on the discovery that only a select subset of such block copolymers of relatively low molecular weight and relatively high hydrophobic block polymer content exist as clear solutions at, or about, 5° C. to 25° C. in water but, when the temperature is raised to about body temperature (typically 37° C. for humans), spontaneously interact to form semisolid hydrogels (i.e., gels) that contain high percentages of water entrapped within the gel network, yet are substantially insoluble in water.

BACKGROUND OF THE INVENTION AND SUMMARY OF PRIOR ART

Recently, many peptide/protein drugs, effective for a variety of therapeutic applications, have become commercially available through advances in recombinant DNA and other technologies. However, as polypeptides or proteins, their high molecular weight, degradation in the gastrointestinal tract, and short half-life in the body limits their routes of administration to parenteral administrations such as intravenous or intramuscular and subcutaneous injection. Many peptide drugs are of limited solubility and/or stability in conventional liquid carriers and are therefore difficult to formulate and administer. Also, in many cases, numerous administrations are required to get the expected therapeutic effect for an extended period of time. Long-term controlled delivery of such polypeptides or proteins is essential to provide for practical applications of these medications and to utilize advanced biotechnology derived drugs. Another problem is patient compliance. It is often difficult to get a patient to follow a prescribed dosage regimen, particularly when the prescription is for a chronic disorder and the drug has acute side effects. Therefore, it would be highly desirable to provide a system for the delivery of drugs, and polypeptide and protein drugs in particular, at a controlled rate over a sustained period of time, without the above mentioned problems, in order to optimize the therapeutic efficacy, minimize the side effects and toxicity, and thereby increase the efficacy and patient compliance.

Drug loaded polymeric devices and dosage forms have been investigated for long term, therapeutic treatment of different diseases. An important property of the polymer is biodegradability, meaning that the polymer can break down or degrade within the body to nontoxic components either concomitant with the drug release, or, after all drug has been released. Furthermore, techniques, procedures, solvents and other additives used to fabricate the device and load the drug should result in dosage forms that are safe for the patient, minimize irritation to surrounding tissue, and be a compatible medium for the drug. Currently, biodegradable implantable controlled release devices are fabricated from solid polymers such as polyglycolic acid, polylactic acid, or copolymers of glycolic and lactic acid. Due to the hydrophobic properties of these polymers, drug loading and device fabrication using these materials requires organic solvents, for example, methylene chloride, chloroform, acetic acid or dimethyl formamide. Obviously, due to the toxic nature of some solvents, extensive drying is generally required after this process. In most cases, the final polymeric device is fabricated in a distinct solid shape (e.g., sphere, slab or rod) requiring implantation that is often accompanied by the trauma of a surgical procedure.

Currently, there are few synthetic or natural polymeric materials which can be used for the controlled delivery of drugs, including peptide and protein drugs, because of the strict regulatory compliance requirements, such as biocompatibility, clearly defined degradation pathway and safety of the degradation products. The most widely investigated and advanced biodegradable polymers in regard to available toxicological and clinical data are the aliphatic poly(α-hydroxy acids), such as poly(D,L- or L- lactic acid) (PLA) and poly(glycolic acid) (PGA) and their copolymers (PLGA). These polymers are commercially available and are presently being used as bioresorbable sutures. An FDA-approved system for controlled release of leuprolide acetate, the Lupron Depot™, is also based on PLGA copolymers. The Lupron Depot™ consists of injectable microspheres, which release leuprolide acetate over a prolonged period (e.g., about 30 days) for the treatment of prostate cancer. Based on this history of use, PLGA copolymers have been the materials of choice in the initial design of parenteral controlled release drug delivery systems using a biodegradable carrier.

Even though there has been some limited success, these polymers also have problems associated with their physicochemical properties and methods of fabrication. Hydrophilic macromolecules, such as polypeptides, cannot readily diffuse through hydrophobic matrices or membranes of polylactides. Drug loading and device fabrication using PLA and PLGA often requires toxic organic solvents, and the solid dosage form may mechanically induce tissue irritation.

A. S. Sawhney and J. A. Hubbell, J. Biomed. Mat. Res., 24, 1197–1411 (1990), synthesized terpolymers of D,L-lactide, glycolide and ϵ-caprolactone which degrade rapidly in vitro. For example, a terpolymer composition of 60% glycolide, 30% lactide, and 10% ϵ-caprolactone exhibited a half-life of 17 days. The hydrophilicity of the material was increased by copolymerization with a poloxamer surfactant (Pluronic F-68). This poloxamer is a block copolymer comprising about 80% by weight of a relatively hydrophobic poly(oxypropylene) block and 20% by weight of a hydrophilic poly(oxyethylene) block. Copolymerization with the poloxamer resulted in a stronger and partly crystalline material which was mechanically stable at physiological temperatures (e.g. 37° C.) in water. The half-life of this copolymer was slightly increased compared to the base polymer. However, it is known that poloxamer-type surfactants are not biodegradable.

An optimum material for use as an injectable or implantable polymeric drug delivery device should be biodegradable, compatible with hydrophilic or hydrophobic drugs, and allow fabrication with simple, safe solvents, such as water, and not require additional polymerization or other covalent bond forming reactions following administration.

One system, which can be fabricated in aqueous solution, is a class of block copolymers referenced above and marketed under the Pluronic™ tradename. These copolymers are composed of two different polymer blocks, i.e. hydrophilic poly(oxyethylene) blocks and hydrophobic poly (oxypropylene) blocks to make up a triblock of poly (oxyethylene)-poly(oxypropylene)-poly(oxyethylene). The triblock copolymers absorb water to form gels which exhibit reverse thermal gelation behavior. However, the Pluronic™ system is nonbiodegradable and the gel properties (water soluble gel) and drug release kinetics (very rapid) from those gels have not proven useful and are in need of substantial improvement.

There is a strong need for hydrophilic biodegradable materials which can be used to incorporate water soluble polypeptide drugs in solution. A. S. Sawhney et al., Macromolecules, Vol 26, No. 4, 581–589 (1993) synthesized macromers having a polyethylene glycol central block, extended with oligomers of α-hydroxy acids such as oligo (D,L-lactic acid) or oligo(glycolic acid) and terminated with acrylate groups. Using nontoxic photoinitiators, these macromers can be rapidly polymerized with visible light. Due to the multifunctionality of the macromers, polymerization results in the formation of crosslinked gels. The gels degrade upon hydrolysis of the oligo(α-hydroxy acid) regions into polyethylene glycol, the α-hydroxy acid, and oligo(acrylic acid), and their degradation rates can be tailored by appropriate choice of the oligo(α-hydroxy acid) from less than 1 day to up to 4 months. However, in this system, a photoinitiator, an additional component, is employed as well as an additional covalent bond-forming photocrosslinking reaction. Highly variable person-to-person performance would result with this approach due to interperson differences in skin thickness and opacity.

Okada et al., Japanese Patent 2-78629 (1990), synthesized biodegradable block copolymeric materials by transesterification of poly(lactic acid) (PLA) or poly(lactic acid)/glycolic acid (PLGA) and polyethylene glycol (PEG). The molecular weight range for PLGA was 400 to 5,000 and for PEG, 200 to 2,000. The mixture was heated at 100 to 250° C. for 1 to 20 hours under a nitrogen atmosphere. The product was miscible with water and formed a hydrogel, however, it precipitated in water above room temperature. In other words, the water solubility and interpolymer chain interactions changed with temperature. This polymer is similar to the polymers described in the Churchill patents discussed below and is utilized as an aqueous suspension or molded into a solid block for implantation. There is no indication that this polymer exhibits properties of reverse thermal gelation so as to be injected as a solution instead of as a colloidal suspension of polymer.

T. Matsuda, ASAIO Journal, M512–M517 (1993) used a biodegradable polymeric gel to deliver a potent peptidyl antiproliferative agent, angiopeptin, to prevent the myointimal hyperplasia that occurs when a diseased vessel is replaced with an artificial graft or treated by an intravascular device. A highly viscous liquid of a block copolymer composed of poly(lactic acid) and polyethylene glycol (PLA-PEG) block segments was used as an in situ coatable drug carrier. The materials were supplied by Taki Chemical Co., Ltd., Hyogo, Japan. A prolonged slow release of angiopeptin from the polymer gel, consisting of 0.5 g PLA-PEG and 0.5 mg angiopeptin, was observed in vitro over a few weeks when the gel was kept in a buffer solution maintained at 37° C. No early burst release of angiopeptin was observed. Based on these results, the local sustained angiopeptin release from the biodegradable polymeric gel coated onto an injured vessel in vivo was theorized to be effective.

L. Martini et al., J. Chem. Soc., Faraday Trans., 90(13), 1961–1966 (1994) synthesized very low molecular weight ABA type triblock copolymers by incorporating hydrophobic poly(ε-caprolactone) which is known to be subject to degradation in vivo by hydrolytic chain scission involving the ester linkages and reported the solution properties of the PCL-PEG-PCL block copolymers. Clouding was observed visually when an aqueous solution of the block copolymers was slowly heated. The cloud points of 2 wt % aqueous solutions of the copolymers were 65° C. and 55° C. for PCL-PEG-PCL (450:4000:450) and PCL-PEG-PCL (680:4000:680), respectively. Reversible gelation on cooling solutions of PCL-PEG-PCL (680:4000:680) was observed at critical concentrations and temperatures ranging from 13% at 25° C. to 30% at 80° C. No lower gel/sol transition was observed on further cooling the solutions to 0° C. The in vitro degradation rate of PCL-PEG-PCL (680:4000:680) was very slow. Only ca. 20% decrease in molar mass (from GPC) was observed over a 16 week period. Such slow degradation is insufficient for a practical drug delivery vehicle.

Churchill et al, U.S. Pat. Nos. 4,526,938 and 4,745,160 show copolymers that are either self-dispersible or can be made self-dispersible in aqueous solutions. These copolymers are ABA triblock or AB block copolymers composed of hydrophobic A-blocks, such as polylactide or poly (lactide-co-glycolide), and hydrophilic B-blocks, such as polyethylene glycol or polyvinyl pyrrolidone. Preferably, to be self-dispersible in water without the use of organic solvents, these polymers must contain more than 50% by weight of hydrophilic (B-block) component as compared to hydrophobic (A block) component or, are copolymers where the hydrophobic component (A block) has a weight average molecular weight of less than 5,000. Although polymers having a weight average molecular weight as low as 1000 are mentioned, there is no direct teaching of such polymers, or that ABA type polymers having a molecular weight of less than 5000 are functional. Further, there is no exemplification of ABA type polymers other than high molecular weight polymers having a hydrophobic content of at least 50% by weight. There is no indication that these block copolymers are soluble in aqueous solutions at any temperature without the use of organic solvents, nor is there any indication that drug/polymers can be administered as a solution. Rather, administration is disclosed as a colloidal suspension of the polymer, or, drug/polymer dispersions are freeze dried into a powder and processed by compression molding to form a solid suitable for use as an implantable depot formulation. Aqueous drug/polymer suspensions or dispersions are two phase systems wherein the dispersed polymer phase is suspended in the continuous aqueous phase. Such dispersions are not suitable for use in situations where sterile filtering processes are required to remove bacterial or other toxic particulates, as any such process would also remove the drug/polymer particles and result in subtherapeutic doses. ABA-type block copolymers that are water soluble and thermally gel are not included in the Churchill, et.al., patents.

From the above it is to be observed that known thermally reversible gels (e.g., Pluronics™) are not inherently useful as drug delivery systems. Although, there are block copolymers that possess reverse thermal gelation properties, these gels lack critical characteristics necessary for control of drug release over a sustained period and present toxicity or biocompatibility issues owing to their non-biodegradability. Thus, while the property of reverse thermal gelation is universally recognized as unique and potentially highly useful in the field of drug delivery, there has yet to be a system developed that possesses the properties necessary for a viable system.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide low molecular weight triblock copolymer drug delivery systems that are biodegradable, exhibit reverse thermal gelation behavior, namely, exist as a liquid solution at low temperatures and reversibly form gels at physiologically relevant temperatures, and provide good drug release characteristics.

A further object of this invention is to provide a drug delivery system for the parenteral administration of hydrophilic and hydrophobic drugs, peptide and protein drugs, and oligonucleotides.

Yet another object of this invention is to provide a method for the parenteral administration of drugs in a biodegradable

polymeric matrix resulting in the formation of a gel depot within the body from which the drugs are released at a controlled rate.

These and other objects are accomplished by means of a biodegradable ABA type block copolymer having an average molecular weight of between about 3100 and 4500 consisting of about 51 to 83% by weight of a hydrophobic A block consisting of a poly(lactide-co-glycolide) block copolymer, and about 17 to 49% by weight of a hydrophilic B polymer block consisting of a polyethylene glycol. Polyethylene glycol (PEG) is also sometimes referred to as poly(ethylene oxide) (PEO) or poly(oxyethylene) and the terms can be used interchangeably for the purposes of this invention. In the hydrophobic A-block, the lactate content is between about 65 to 85 mole percent and the glycolate content is between about 15 and 35 mole percent.

Additional objects and advantages will become apparent from the following summary and detailed description of the various embodiments making up this invention.

As used herein the following terms shall have the assigned meanings:

"Parenteral" shall mean intramuscular, intraperitoneal, intra-abdominal, subcutaneous, and, to the extent feasible, intravenous and intraarterial.

"Gelation temperature", means the temperature at which the biodegradable block copolymer undergoes reverse thermal gelation, i.e. the temperature below which the block copolymer is soluble in water and above which the block copolymer undergoes phase transition to increase in viscosity or to form a semi-solid gel.

The terms "gelation temperature" and "reverse thermal gelation temperature" or the like shall be used interchangeably in referring to the gelation temperature.

"Polymer solution", "aqueous solution" and the like, when used in reference to a biodegradable block copolymer contained in such solution, shall mean a water based solution having such block copolymer dissolved therein at a functional concentration, and maintained at a temperature below the gelation temperature of the block copolymer. "Reverse thermal gelation" is the phenomena whereby a solution of a block copolymer spontaneously increases in viscosity, and in many instances transforms into a semisolid gel, as the temperature of the solution is increased above the gelation temperature of the copolymer. For the purposes of the invention, the term "gel" includes both the semisolid gel state and the high viscosity state that exists above the gelation temperature. When cooled below the gelation temperature, the gel spontaneously reverses to reform the lower viscosity solution. This cycling between the solution and the gel may be repeated ad infinitum because the sol/gel transition does not involve any change in the chemical composition of the polymer system. All interactions to create the gel are physical in nature and do not involve the formation or breaking of covalent bonds.

"Drug delivery liquid" or "drug delivery liquid having reverse thermal gelation properties" shall mean a polymer solution that contains drug (the drug per se can either be dissolved or colloidal) suitable for administration to a warm-blooded animal which forms a gelled drug depot when the temperature is raised to or above the gelation temperature of the block copolymer.

"Depot" means a drug delivery liquid following administration to a warm-blooded animal which has formed a gel upon the temperature being raised to or above the gelation temperature.

"Gel", means the semi-solid phase that spontaneously occurs as the temperature of the "polymer solution" or "drug delivery liquid" is raised to or above the gelation temperature of the block copolymer.

"Aqueous polymer composition" means either a drug delivery liquid or a gel comprised of the water phase having uniformly contained therein a drug and the biodegradable block copolymer. At temperatures below the gelation temperature the copolymer may be soluble in the water phase and the composition will be a solution. At temperatures at or above the gelation temperature the copolymer will solidify to form a gel with the water phase and the composition will be a gel or semi-solid.

"Biodegradable" means that the block copolymer can chemically break down or degrade within the body to form nontoxic components. The rate of degradation can be the same or different from the rate of drug release.

"Drug" shall mean any organic or inorganic compound or substance having bioactivity and adapted or used for a therapeutic purpose. Proteins, oligonucleotides, DNA, and gene therapies are included under the broader definition of drug.

"Peptide", "polypeptide", "oligopeptide" and "protein" shall be used interchangeably when referring to peptide or protein drugs and shall not be limited as to any particular molecular weight, peptide sequence or length, field of bioactivity or therapeutic use unless specifically stated.

"Poly(lactide-co-glycolide)" shall mean a copolymer derived from the condensation copolymerization of lactic acid and glycolic acid, or, by the ring opening polymerization of α-hydroxy acid precursors, such as lactide or glycolide. The terms "lactide" and "lactate" and "glycolide" and "glycolate" are used interchangeably.

Therefore, the present invention is based on the discovery that ABA-type block copolymers, where the A-blocks are a relatively hydrophobic poly(lactide-co-glycolide) and the B-block is a relatively hydrophilic polyethylene glycol, having a hydrophobic content of between about 51 to 83% by weight and an overall block copolymer molecular weight of between about 3100 and 4500, exhibit water solubility at low temperatures and undergo reversible thermal gelation at mammalian physiological body temperatures. At such high hydrophobic content it is unexpected that such block copolymers would be water soluble. It is generally taught that any polymer having a hydrophobic content in excess of 50% by weight is substantially insoluble in water and can only be made appreciably soluble in aqueous systems, if at all, when a certain amount of an organic cosolvent has been added.

Therefore, basic to the present invention is the utilization of ABA-type block copolymers having hydrophobic PLGA A-block segments and hydrophilic PEG B-block segments according to the formula:

PLGA-PEG-PLGA

wherein the block copolymers that have utility as disclosed in this invention meet the criteria summarized in Table 1, namely, compositional make-up within the indicated ranges that result in block copolymers that demonstrate the desired reverse thermal gelling behavior. For purposes of disclosing molecular weight parameters, all reported molecular weight values are based on measurements by NMR or GPC (gel permeation chromatography) analytical techniques. The reported weight average molecular weights and number average molecular weights were determined by GPC and NMR respectively. The reported lactide/glycolide ratio was calculated from NMR data. GPC analysis was performed on a Styragel HR-3 column calibrated with PEG using RI detection and chloroform as the eluent. NMR spectra were taken in $CDCl_3$ on a Bruker 200 Mz instrument.

TABLE 1

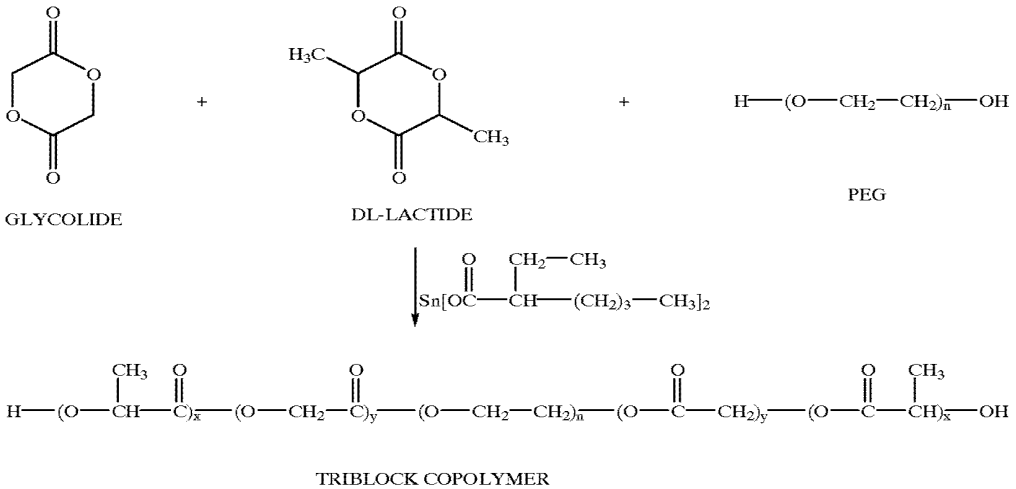
Total molecular weight:	3100 to 4500
PEG content:	17 to 49% by weight
Total PLGA content:	51 to 83% by weight
Lactate content:	65 to 85 mole percent
Glycolate content:	15 to 35 mole percent
Behavior:	water soluble below the gelation temperature; gels above the gelation temperature

The biodegradable, hydrophobic A-block segments are poly(α-hydroxy acids) derived or selected from the group consisting of poly(D,L-lactide-co-glycolide) and poly(L-lactide-co-glycolide), which are referred to collectively as poly(lactide-co-glycolide) in the present invention. Assuming that the average molecular weight of each of the A-blocks in an ABA triblock copolymer is essentially the same, the average molecular weight of each poly(lactide-co-glycolide) polymeric A block is between about 800 and 1800.

The hydrophilic B-block segment is preferably polyethylene glycol (PEG) having an average molecular weight of between about 600 and 2200.

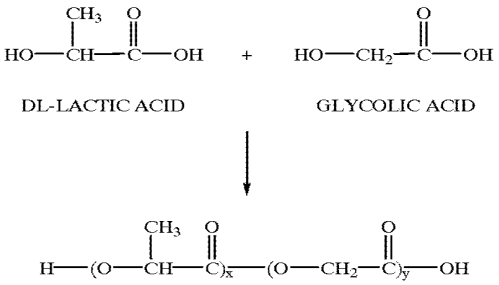
The triblock copolymer may be synthesized by ring opening polymerization, or condensation polymerization according to the following reaction schemes:

SYNTHESIS BY RING OPENING POLYMERIZATION

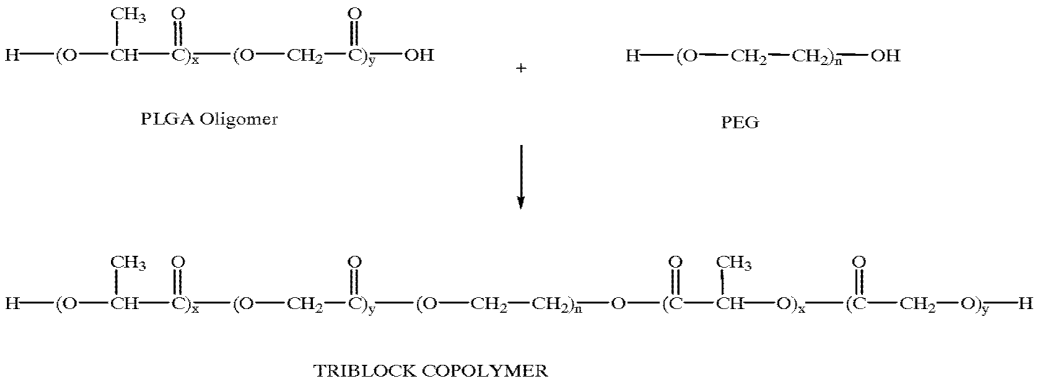


SYNTHESIS BY CONDENSATION POLYMERIZATION

Step 1: Synthesis of PLGA Oligomer



Step 2: Synthesis of ABA Block copolymer



The hydrophilic B-block is formed from appropriate molecular weights of PEG. PEG was chosen as the hydrophilic, water-soluble block because of its unique biocompatibility, nontoxicity, hydrophilicity, solubilization properties, and rapid clearance from a patient's body.

The hydrophobic A-blocks are synthesized and utilized because of their biodegradable, biocompatible, and solubilization properties. The in vitro and in vivo degradation of these hydrophobic poly(lactide-co-glycolide) A-blocks is well understood and the degradation products are naturally occurring compounds that are readily metabolized and/or eliminated by the patient's body.

Surprisingly, the total weight percentage of the hydrophobic poly(lactide-co-glycolide) A-blocks, relative to that of the hydrophilic PEG B-block, is high, e.g. between about 51 to 83% by weight, and most preferably between about 65 to 78% by weight, yet the ABA copolymer retains the desirable water solubility and reverse thermal gelation properties. It is an unexpected discovery that a block copolymer with such a large proportion of hydrophobic component would be water soluble below normal room temperatures such as refrigerator temperatures (5° C). It is believed the desirable solubility character is possible due to maintaining the overall low molecular weight of the entire ABA block copolymer between about 3,100 and 4,500. Thus, water soluble biodegradable block copolymers possessing thermally reversible gelation properties are prepared wherein the hydrophilic B-block makes up about 17 to 49% by weight of the copolymer and the hydrophobic A-blocks make up about 51 to 83% by weight of the copolymer. In a preferred embodiment, the PLGA A-blocks may comprise between about 65 to 78% by weight of the copolymer and the PEG B-block may comprise between about 22 to 35% by weight of the copolymer. Further, the preferred overall average molecular weight of the entire ABA block copolymer will be between about 3500 and 4100.

The concentration at which the block copolymers are soluble at temperatures below the gelation temperature may be considered as the functional concentration. Generally speaking, block copolymer concentrations of as low as 3% and of up to about 50% by weight can be used and still be functional. However, concentrations in the range of about 5 to 40% are preferred and concentrations in the range of about 10–30% by weight are most preferred. In order to obtain a viable gel phase transition with the copolymer, a certain minimum concentration, e.g. 3% by weight is required. At the lower functional concentration ranges the phase transition may result in the formation of a weak gel. At higher concentrations, a strong gel network is formed.

The mixture of the biodegradable copolymer and peptide/protein drugs, and/or other types of drugs, may be prepared as an aqueous solution of the copolymer below the gelation temperature to form a drug delivery liquid where the drug may be either partially or completely dissolved. When the drug is partially dissolved, or, when the drug is essentially insoluble, the drug exists in a colloidal state such as a suspension or emulsion. This drug delivery liquid is then administered parenterally, topically, transdermally or inserted into a cavity such as by ocular, vaginal, transurethral, rectal, nasal, oral, or aural administration to a patient whereupon it will undergo a reversible thermal gelation since body temperature will be above the gelation temperature.

This system will cause minimal toxicity and minimal mechanical irritation to the surrounding tissue due to the biocompatibility of the materials and pliability of the gel, and will completely biodegrade to lactic acid, glycolic acid, and PEG within a specific time interval. The drug release, gel strength, gelation temperature and degradation rate can be controlled by proper design and preparation of the various copolymer blocks, namely, through modifications of the weight percent of the A-blocks and B-block, the mole percentages of lactate and glycolate, and the molecular weight and polydispersity of the ABA triblock copolymer. Drug release is also controllable through adjustment of the concentration of polymer in the drug delivery liquid.

A dosage form comprised of a solution of the block copolymer that contains either dissolved drug or drug as a suspension or emulsion is administered to the body. This formulation then spontaneously gels due to the reverse thermal gelation properties of the block copolymer to form a drug depot as the temperature of the formulation rises to body temperature. The only limitation as to how much drug can be loaded into the formulation is one of functionality, namely, the drug load may be increased until the thermal gelation properties of the copolymer are adversely affected to an unacceptable degree, or until the properties of the formulation are adversely affected to such a degree to make administration of the formulation unacceptably difficult. Generally speaking, it is anticipated that in most instances the drug will make up between about 0.01 to 20% by weight of the formulation with ranges of between about 0.01 to 10% highly common. These ranges of drug loading are not limiting to the invention; drug loadings outside of these ranges fall within the scope of the invention.

A distinct advantage to the compositions of the invention lies in the ability of the block copolymer to increase the

solubility of many drug substances. The combination of the hydrophobic A-blocks and hydrophilic B-block render the block copolymer amphiphilic in nature. In that regard it functions much as a soap or surfactant in having both hydrophilic and hydrophobic properties. This is particularly advantageous in the solubilization of hydrophobic or poorly water soluble drugs such as cyclosporin and paclitaxel. What is surprising is the degree of drug solubilization of most, if not all, drugs since the major component of the block copolymer is the hydrophobic A-blocks. However, as already discussed, even though the hydrophobic copolymer blocks are the major component the block copolymer is water soluble and it has been found that there is an additional increase in drug solubility when combined in an aqueous phase of the block copolymer.

Another advantage to the composition of the invention lies in the ability of the block copolymer to increase the chemical stability of many drug substances. Various mechanisms for degradation of drugs that lead to a drug's chemical instability have been observed to be inhibited when the drug is in the presence of the block copolymer. For example, paclitaxel and cyclosporin A are substantially stabilized in the aqueous polymer composition of the present invention relative to certain aqueous solutions of these same drugs in the presence of organic co-solvents. This stabilization effect on paclitaxel and cyclosporin A is but illustrative of the effect that would be achieved with many other drug substances.

In certain situations the drug loaded polymer may be administered in the gel state instead of as a solution. The gelation may be the result of raising the temperature of a drug laden polymer solution above the gelation temperature of the polymer prior to administration or caused by raising the concentration of the polymer in the solution above the saturation concentration at the temperature of administration. In either event, the gel thus formed may be administered parenterally, topically, transdermally or inserted into a cavity such as by ocular, vaginal, transurethral, rectal, nasal, oral, or aural administration.

This invention is applicable to bioactive agents and drugs of all types and offers an unusually effective way to deliver polypeptides and proteins. Many labile peptide and protein drugs are amenable to formulation into the block copolymers of the invention and can benefit from the reverse thermal gelation process described herein. While not specifically limited to the following, examples of pharmaceutically useful polypeptides and proteins may be selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinizing hormone releasing hormone, growth hormone (human, porcine, bovine, etc.), growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α,β, or γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), interleukin-11 (IL-11), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins and synthetic analogues, modifications and pharmacologically active fragments thereof, enzymes, cytokines, monoclonal antibodies and vaccines.

The only limitation to the polypeptide or protein drug which may be utilized is one of functionality. In some instances, the functionality or physical stability of polypeptides and proteins can also be increased by various additives to aqueous solutions or suspensions of the polypeptide or protein drug. Additives, such as polyols (including sugars), amino acids, surfactants, polymers, other proteins and certain salts may be used. These additives can readily be incorporated into the block copolymers which will then undergo the reverse thermal gelation process of the present invention.

Developments in protein engineering may provide the possibility of increasing the inherent stability of peptides or proteins. While such resultant engineered or modified proteins may be regarded as new entities in regards to regulatory implications, that does not alter their suitability for use in the present invention. One of the typical examples of modification is PEGylation where the stability of the polypeptide drugs can be significantly improved by covalently conjugating water-soluble polymers such as polyethylene glycol with the polypeptide. Another example is the modification of the amino acid sequence in terms of the identity or location of one or more amino acid residues by terminal and/or internal addition, deletion or substitution Any improvement in stability enables a therapeutically effective polypeptide or protein to be continuously released over a prolonged period of time following a single administration of the drug delivery liquid to a patient.

In addition to peptide or protein based drugs, other drugs from all therapeutic and medically useful categories may be utilized. These drugs are described in such well-known literature references as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics. A brief listing of specific agents is provided for illustration purposes only, and shall not be deemed as limiting: anti-cancer agents such as mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D and camptothecin; benzodiazepine antipsychotics such as olanzapine; antibacterials such as cefoxitin, anthelmintics such as ivermectin, antivirals such as acyclovir, immunosupressants such as cyclosporin A (cyclic polypeptide-type agent), steroids, and prostaglandins.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects, features and advantages of the invention will become apparent from a consideration of the following detailed description presented in connection with the accompanying drawings in which:

FIG. **1** is a phase diagram illustrating the gelation behavior of aqueous solutions of a PLGA-PEG-PLGA triblock copolymer, studied at different concentrations and temperatures.

FIGS. **2***a*–**2***c* are degradation profiles illustrating the in vitro degradation of a PLGA-PEG-PLGA triblock copolymer incubated at different temperatures and pH's.

FIG. **3** is a graph illustrating the continuous release of insulin over a sustained period of time from a PLGA-PEG-PLGA triblock copolymer thermal gel.

FIG. **4** is a release profile of paclitaxel from a PLGA-PEG-PLGA triblock copolymer thermal gel formulation showing the cumulative controlled release of the paclitaxel for approximately 50 days.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

In order to illustrate preferred embodiments of this invention, the syntheses of low molecular weight ABA block

copolymers consisting of 75% by weight hydrophobic A-blocks (poly(lactide-co-glycolide); (PLGA)), and 25% by weight hydrophilic B-block (polyethylene glycol; (PEG)) were completed. The object was the preparation of PLGA-PEG-PLGA triblock copolymers having an average molecular weight of about 4,000, comprised of two A-blocks each with an average molecular weight of about 1500, and a B-block having an average molecular weight of about 1000. Each A-block would consist of about 75 mole percent lactate and 25 mole percent glycolate.

EXAMPLES

Example 1

Synthesis of PLGA-PEG-PLGA Triblock Copolymer by Ring Opening Copolymerization

Following the reaction scheme given above, PEG (Mw=1000) was dried by azeotropic distillation in a flask with toluene (2×75 ml) under an atmosphere of nitrogen followed by drying at 130° C. under vacuum (5 mm Hg). Lactide and glycolide monomers (in mole ratios of 3:1, respectively) were added to the flask followed by the addition of stannous octoate (0.1 wt %) and the reaction mixture was heated at 150° C. under vacuum (5 mm Hg). The progress of the reaction was followed by GPC (gel permeation chromatography). After an appropriate time, the reaction was stopped and the flask was cooled to room temperature. The residue was dissolved in cold water and heated to 70–80° C. to precipitate the polymer formed. The supernatant was decanted and the polymer residue was again dissolved in cold water and heated to induce precipitation. This process of dissolution followed by precipitation was repeated three times. Finally, the polymer was dissolved in a minimum amount of water and lyophilized.

The resulting PLGA-PEG-PLGA copolymer had a weight average molecular weight (Mw) of 3737, a number average molecular weight (Mn) of 2928 and an Mw/Mn ratio of 1.3.

Example 2

Synthesis of PLGA-PEG-PLGA Triblock Copolymer by Condensation Copolymerization

Into a three necked flask, equipped with a nitrogen inlet, thermometer, and distillation head for removal of water, was placed DL-lactic acid and glycolic acid (3:1 mole ratio, respectively). The reaction mixture was heated at 160° C. under nitrogen with stirring at atmospheric pressure for three hours and then under reduced pressure (5 mm Hg). The progress of the reaction was followed by GPC. The reaction was stopped at the appropriate time and the polymer formed was purified by precipitation from a dichloromethane solution into a large excess of methanol. The residue was triturated with methanol and dried under vacuum (0.05 mm Hg) at 23° C. The PLGA oligomer was characterized by GPC, IR and NMR. The resulting PLGA oligomer had a weight average molecular weight (Mw) of 9900, a number average molecular weight (Mn) of 5500 and an Mw/Mn ratio of 1.8.

The PLGA was mixed with PEG (Mw=1000) and was heated in a flask at 160° C. under a nitrogen atmosphere. The progress of the reaction was followed by GPC. After an appropriate time, the reaction was stopped and the flask was cooled to room temperature. The residue was dissolved in cold water then heated to 70–80° C. to precipitate the copolymer. The supernatant was decanted and the residue was again dissolved in cold water and heated to precipitate the polymer. This process of dissolution and precipitation was repeated three times. Finally, the polymer was dissolved in a minimum amount of water and lyophilized.

The resulting PLGA-PEG-PLGA block copolymer had a weight average molecular weight (Mw) of 4043, a number average molecular weight (Mn) of 2905 and an Mw/Mn ratio of 1.4. The weight average molecular weights and number average molecular weights were determined by GPC and NMR, respectively. The lactide/glycolide ratio was calculated from NMR data. GPC analysis was performed on a Styragel HR-3 column calibrated with PEG using RI detection and chloroform as the eluent. NMR spectra were taken in $CDCl_3$ on a Bruker 200 MHZ instrument. NMR peak assignments confirmed the triblock ABA structure.

Example 3

The gelation behavior of aqueous solutions of the ABA triblock copolymer of Example 1 was studied at different concentrations. Polymer solutions of 9–30% by weight were prepared in water and the change in viscosity was observed at temperatures ranging between 10° and 60° C. Gelation was defined as the physical state where the polymer solution did not readily flow upon inverting a vial of polymer solution. The phase diagram (FIG. **1**) of the polymer of Example 1 as a function of temperature and triblock copolymer concentration was generated. The novel, reverse thermal gelation behavior was clearly apparent, and occurred as the triblock copolymer solutions were heated. The gelation at physiologically relevant temperatures (e.g., 37° C.) was particularly prevalent and formed the basis for the substantial utility of the systems for medical and drug delivery purposes.

Example 4

The in vitro degradation of the PLGA-PEG-PLGA triblock copolymer of Example 1 was determined for a 23% by weight solution or gel (1 ml) of copolymer incubated at different temperatures (−10°, 5°, 23° and 37° C.) and at different pH's (3.0, 5.0 and 7.4) over a 30 week period. The degradation and biodegradation of this triblock copolymer was caused by hydrolysis and resulted in lactic acid, glycolic acid and PEG as the final degradation products.

Samples (50 μl) were taken weekly. The samples were lyophilized, dissolved in chloroform, and the molecular weights of the polymer residues were determined by GPC as described previously. The degradation of the polymer was substantially independent of pH over the pH 3.0 to pH 7.4 range. The thermal gelling behavior was also independent of pH over the same pH range. The degradation was more rapid at higher temperatures. The degradation profiles that were generated are shown in FIGS. **2***a*, **2***b* and **2***c*.

Example 5

The in vivo biodegradation of the polymer of Example 1 was determined over a four week period. A 0.40 to 0.45 ml sample of a cold aqueous solution containing 23% by weight triblock copolymer was injected subcutaneously into rats. Upon reaching body temperature, which was above the gelation temperature of the polymer, a gel lump immediately formed which was visibly apparent. Samples were surgically retrieved as a function of time and indicated that the gel became progressively smaller over a two week period. Between two weeks and four weeks the physical state of the injected triblock copolymer changed from a gel, to a mixture of a gel in a viscous liquid, and finally to a viscous liquid containing no gel that was gradually completely resorbed. At the end of the four week period no formulation was visible at the injection site. Microscopically, small pockets of viscous liquid were observable, that also resorbed completely over the following two week period.

Example 6

Paclitaxel and cyclosporin A are hydrophobic drugs that are highly insoluble in water (solubilities were approximately 4 μg/ml). However, these drugs showed significantly higher solubilities when dissolved in aqueous solutions of PLGA-PEG-PLGA triblock copolymer. For example, in a 20% by weight aqueous copolymer solution (polymer of Example 2), paclitaxel was soluble up to 5 mg/ml and cyclosporin A was soluble up to 2 mg/ml.

Paclitaxel and cyclosporin A were highly unstable in aqueous cosolvent solutions (e.g. in water/acetonitrile solutions). The paclitaxel contained in either 20% by weight aqueous PLGA-PEG-PLGA triblock copolymer solutions (i.e., below the gelation temperature of the copolymer) or gels (i.e., above the gelation temperature of the copolymer) was >85% intact after 120 days in storage (5° C. and 37° C.), whereas cyclosporin A was stable over 100 days (5° C.).

Example 7

A 28% by weight aqueous solution of the PLGA-PEG-PLGA triblock copolymer of Example 1 was prepared. Insulin (zinc-free), a parenterally administered protein with proven beneficial effects in the treatment of diabetes mellitus, was suspended in this aqueous solution of triblock copolymer to a final concentration of 5 mg/ml. Approximately 2 ml. of this composition were placed onto a watchglass equilibrated to 37° C. The composition immediately gelled and adhered to the watchglass, whereupon it was placed directly into 10 mM phosphate buffered saline, pH 7.4, 37° C., and the release kinetics of the insulin from the gel were monitored by reversed phase HPLC using UV detection and gradient elution (TFA/acetonitrile/water mobile phase). The data has been graphically summarized in FIG. **3**. Insulin was released in a continuous fashion for approximately one week. The utility of the triblock copolymer thermal gel in the controlled delivery of proteins and peptides for a substantial period was clearly established and illustrated by this Example.

Example 8

To a 23% by weight aqueous solution of the PLGA-PEG-PLGA triblock copolymer of Example 1 was added sufficient paclitaxel to provide approximately 2.0 mg/ml of drug. A 2 ml sample of this solution was put onto a watchglass and equilibrated at 37° C. Since the temperature was greater than the gelation temperature of the copolymer, a gel formed on the watchglass. The watchglass was placed in a 200 ml beaker containing release media comprised of 150 ml of PBS (pH 7.4) containing 2.4% by weight Tween-80 and 4% by weight Cremophor EL equilibrated at 37° C. The solution in the beaker was stirred. The top of the beaker was sealed to prevent evaporation. The whole assembly was placed into an incubator at 37° C. The release study was performed in triplicate. At different time periods a 5 ml aliquot of the release media was taken and analyzed for paclitaxel. The PBS solution was replaced with fresh PBS after each aliquot removal. Samples were collected at 1, 2, 4, 8, 18, and 24 hours, and thereafter at 24 hour intervals, and analyzed by HPLC. The release profile of paclitaxel from the gel is shown in FIG. **4**. The gel formulation provided excellent control over the release of the paclitaxel for approximately 50 days.

The above description will enable one skilled in the art to make PLGA-PEG-PLGA block copolymers that form aqueous solutions having reverse thermal gelation properties and to utilize the same in the field of drug delivery. Although the controlled delivery of both a conventional drug (paclitaxel) and a protein drug (insulin) were successfully achieved and presented in the Examples, these descriptions are not intended to be an exhaustive statement of all drugs which can be utilized and loaded into the biodegradable block copolymers. Certainly, numerous other drugs from all classes of therapeutic agents are well suited for delivery from the PLGA-PEG-PLGA block copolymers as described in the invention. Neither are all block copolymers which may be prepared, and which demonstrate the critical reverse thermal gelation property, specifically shown. However, it will be immediately apparent to one skilled in the art that various modifications may be made without departing from the scope of the invention which is limited only by the following claims and their functional equivalents.

We claim:

1. An aqueous biodegradable polymeric drug delivery composition possessing reverse thermal gelation properties comprised of an aqueous phase having uniformly contained therein:

(a) an effective amount of a drug; and

(b) a biodegradable ABA-type block copolymer of the formula:

PLGA-PEG-PLGA

where PLGA is a hydrophobic poly(lactide-co-glycolide) copolymer that comprises the A-blocks and PEG is a hydrophilic polyethylene glycol polymer that comprises the B-block, said block copolymer having an average molecular weight of between about 3100 and 4500 wherein, in the block copolymer, the PLGA A-blocks comprise about 51 to 83% by weight of said copolymer and the PEG B-block comprises about 17 to 49% by weight of said copolymer.

2. An aqueous polymeric composition according to claim **1** wherein the block copolymer content of said composition is between about 3 and 50% by weight.

3. An aqueous polymeric composition according to claim **2** wherein the PLGA copolymer A-block comprises between about 65 to 85 mole percent lactide and between about 15 and 35 mole percent glycolide.

4. An aqueous polymeric composition according to claim **3** wherein the block copolymer comprises between about 65 to 78% by weight of said hydrophobic PLGA A-blocks and between about 22 to 35% by weight of said hydrophilic PEG B-block.

5. An aqueous polymeric composition according to claim **4** wherein the block copolymer has an average molecular weight of between about 3500 and 4100.

6. An aqueous polymeric composition according to claim **3** wherein said drug is a polypeptide or protein.

7. An aqueous polymeric composition according to claim **6** wherein said polypeptide or protein is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinizing hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α, interferon-β, interferon-γ, -; gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP),

hANP, glucagon-like peptide (GLP-1), interleukin-11 (IL-11), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, monoclonal antibodies and vaccines.

8. An aqueous polymeric composition according to claim **13** wherein the drug content of said composition is between about 0.01 and 20% by weight.

9. An aqueous polymeric composition according to claim **9** wherein said drug is an anti-cancer or anti-cell proliferation agent.

10. An aqueous polymeric composition according to claim **9** wherein said drug is an anti-cancer agent selected from the group consisting of mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D, and camptothecin.

11. An aqueous polymeric composition according to claim **10** wherein the drug content of said composition is between about 0.01 and 20% by weight.

12. A method for the administration of a drug to a warm blooded animal in a controlled release form which comprises:

(1) providing an aqueous biodegradable polymeric drug delivery composition possessing reverse thermal gelation properties comprised of an aqueous phase having uniformly contained therein:

(a) an effective amount of a drug; and

(b) a biodegradable ABA-type block copolymer of the formula:

PLGA-PEG-PLGA

where PLGA is a hydrophobic poly(lactide-co-glycolide) copolymer that comprises the A-blocks and PEG is a hydrophilic polyethylene glycol polymer that comprises the B-block, said block copolymer having an average molecular weight of between about 3100 and 4500.

(2) maintaining said composition as a liquid at a temperature below the gelation temperature of said block copolymer; and

(3) administering said composition as a liquid to said warm blooded animal with the subsequent formation of a gel as the temperature of said composition is raised by the body temperature of said animal to be above the gelation temperature of said block polymer.

13. A method according to claim **12** wherein said administration is by parenteral, ocular, topical, transdermal, vaginal, transurethral, rectal, nasal, oral, or aural means.

14. A method according to claim **13** wherein the block copolymer content of said composition is between about 3 and 50% by weight.

15. A method according to claim **14** wherein, in the block copolymer of said composition, the PLGA A-blocks comprises about 51 to 83% by weight of said copolymer and the PEG B-block comprises about 17 to 49% by weight of said copolymer.

16. A method according to claim **15** wherein, in the block copolymer of said composition, the PLGA copolymer A-block comprises between about 65 to 85 mole percent lactide and between about 15 and 35 mole percent glycolide.

17. A method according to claim **16** wherein, in the block copolymer of said composition, the PLGA A-blocks comprises between about 65 to 78% by weight of said copolymer and the PEG B-Block comprises between about 22 to 35% by weight of said copolymer.

18. A method according to claim **15** wherein the block copolymer of said composition has an average molecular weight of between about 3500 and 4100.

19. A method according to claim **15** wherein said drug administered is a polypeptide or protein.

20. A method according to claim **19** wherein said polypeptide or protein is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin or luteinizing hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 (IL-2), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), interleukin-11 (IL-11), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, monoclonal antibodies and vaccines.

21. A method according to claim **19** wherein the drug content of said composition is between about 0.01 and 20% by weight.

22. A method according to claim **15** wherein said drug administered is an anti-cancer or anti-cell proliferation agent.

23. A method according to claim **22** wherein said drug is an anti-cancer agent selected from the group consisting of mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D and camptothecin.

24. A method according to claim **22** wherein the drug content of said composition is between about 0.01 and 20% by weight.

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(54) **PROTEINS DEPOSITED ONTO SPARINGLY SOLUBLE BIOCOMPATIBLE PARTICLES FOR CONTROLLED PROTEIN RELEASE INTO A BIOLOGICAL ENVIRONMENT FROM A POLYMER MATRIX**

(75) Inventors: **Chung Shih**, Sandy, UT (US); **Gaylen Zentner**, Salt Lake City, UT (US); **Ai-Zhi Piao**, Salt Lake City, UT (US)

Correspondence Address:
THORPE NORTH WESTERN
8180 SOUTH 700 EAST, SUITE 200
P.O. BOX 1219
SANDY, UT 84070 (US)

(73) Assignee: **MacroMed, Incorporated**

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(57) **ABSTRACT**

The present invention relates to compositions and methods for the modulated release of one or more proteins or peptides. The composition is comprised of a biocompatible polymeric matrix, a protein and/or peptide, and a sparingly water-soluble or essentially insoluble particle. The protein is deposited by adsorption or some other mechanism onto the sparingly water-soluble biocompatible particle wherein the protein-particle combination is dispersed within the polymeric matrix. The deposition of the protein onto the particle acts to modulate the release of the protein or peptide from dosage forms including long-acting dosage systems.

EXHIBIT D

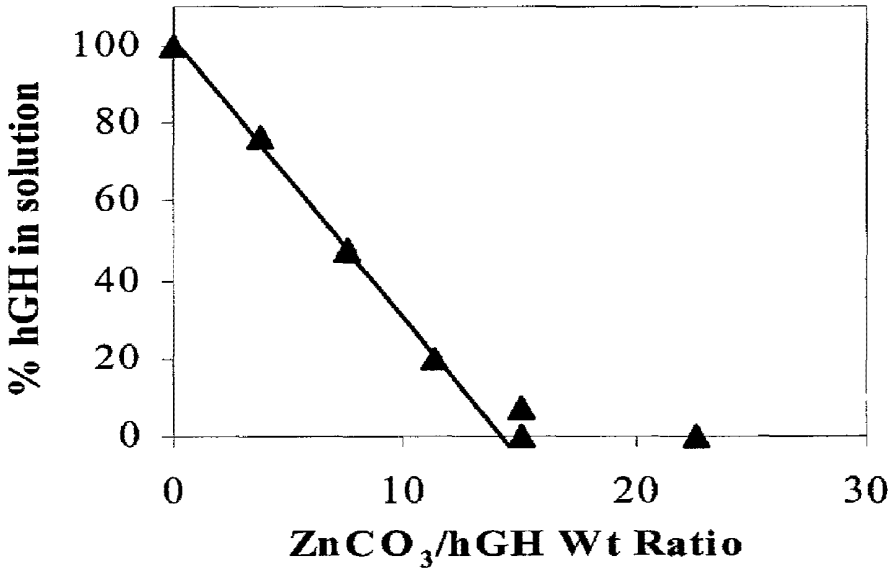

% hGH in solution
100
80
60
40
20
0
0
10
20
30
ZnCO3/hGH Wt Ratio

FIG. 1

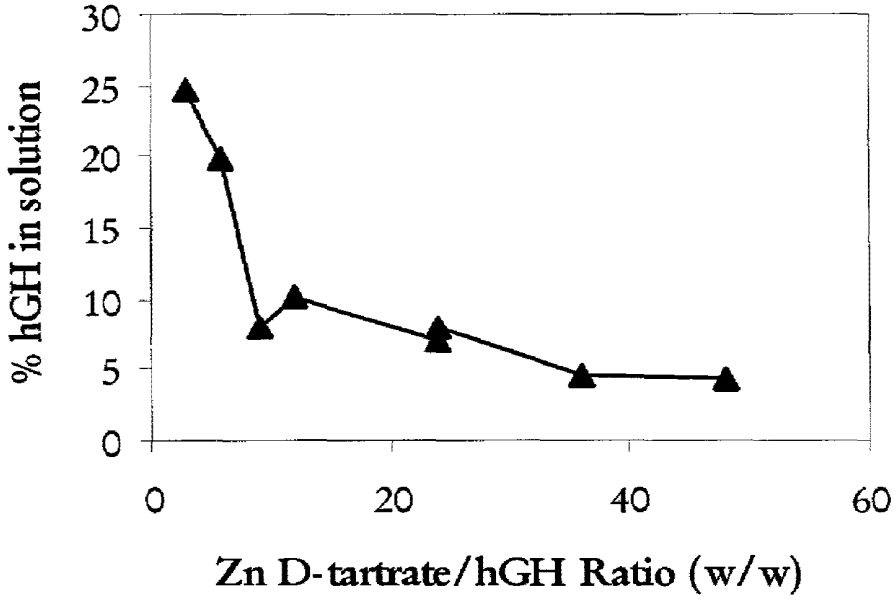

% hGH in solution
30
25
20
15
10
5
0
0
20
40
60
Zn D-tartrate/hGH Ratio (w/w)

FIG. 2

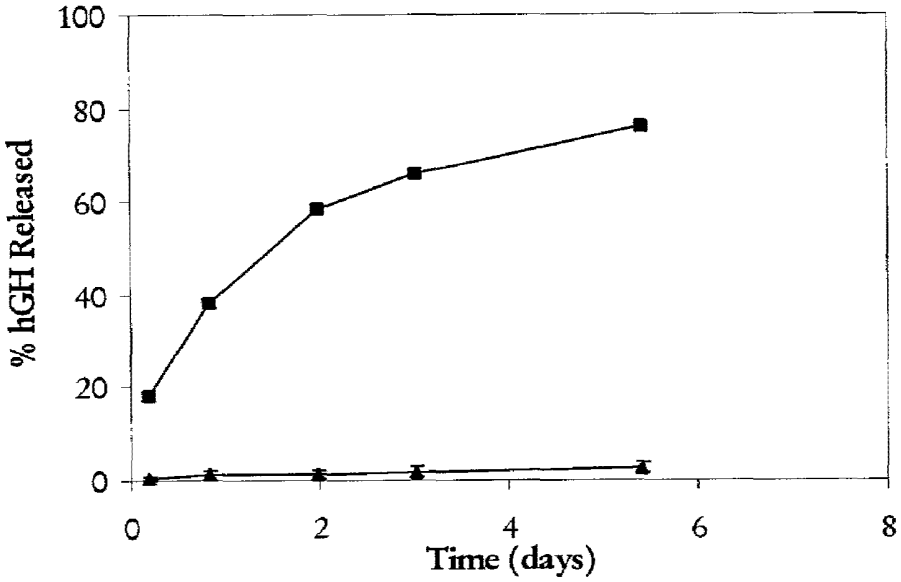

100
80
60
40
20
0
% hGH Released
0
2
4
6
8
Time (days)

FIG. 3

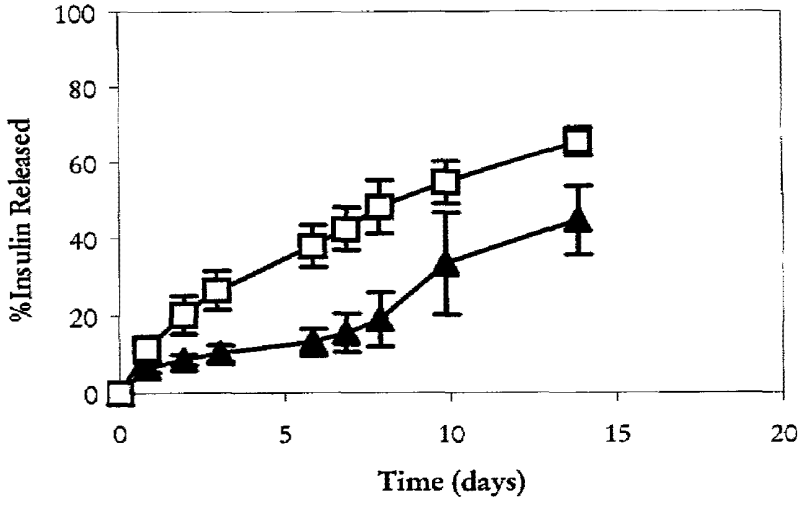

100
80
60
40
20
0
%Insulin Released
0
5
10
15
20
Time (days)

FIG. 4

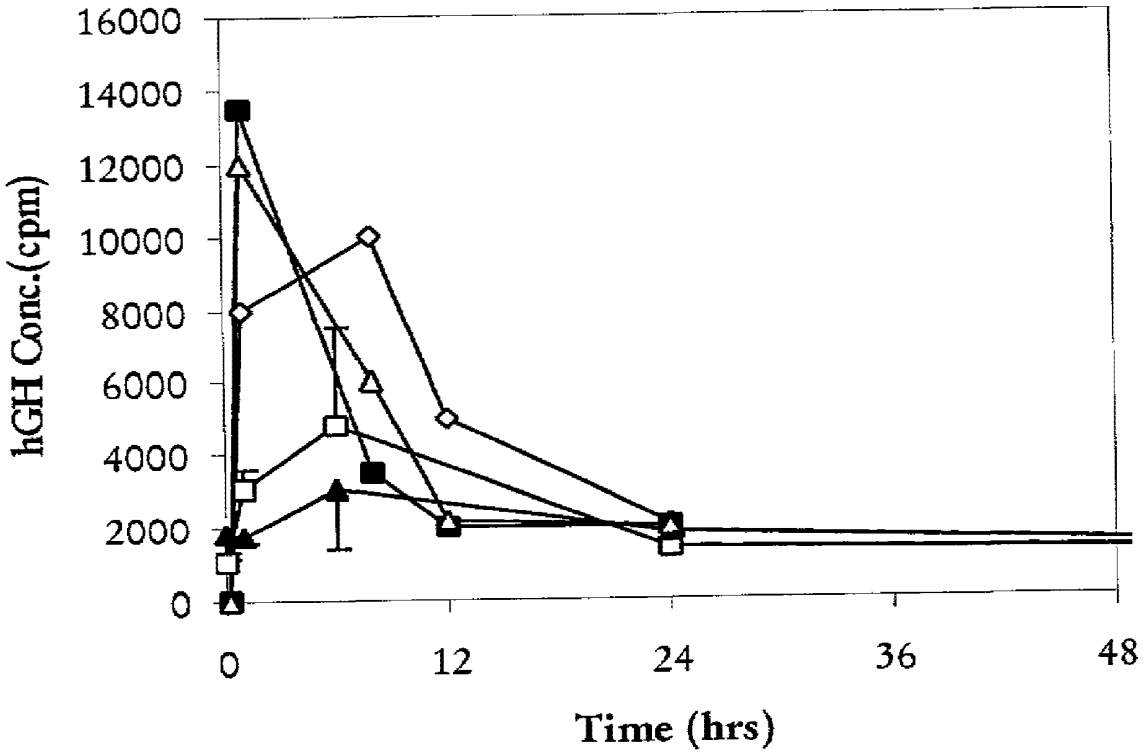

16000
14000
12000
10000
8000
6000
4000
2000
0
hGH Conc.(cpm)
0
12
24
36
48
Time (hrs)

FIG. 5

PROTEINS DEPOSITED ONTO SPARINGLY SOLUBLE BIOCOMPATIBLE PARTICLES FOR CONTROLLED PROTEIN RELEASE INTO A BIOLOGICAL ENVIRONMENT FROM A POLYMER MATRIX

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 60/195,700 filed Apr. 7, 2000.

FIELD OF THE INVENTION

[0002] The present invention is related to compositions and methods for the controlled release of proteins from a drug delivery system. Particularly, by depositing proteins onto sparingly water-soluble or essentially insoluble biocompatible particles including salts and oxides, protein release rates from the dosage forms are reduced.

BACKGROUND OF THE INVENTION

[0003] There have been many approaches to meet the problems of regulating the delivery of proteins or peptides to biological systems or environments in the proper place, at the proper time, and at the proper dose to achieve a desired effect. These systems generally depend on the utilization of physical or chemical stimuli in the surrounding environment. Further, these environmental stimuli are usually of an external nature to the drug delivery system. Mechanisms that respond to such stimuli or signals include protein binding, hydrogel expanding or swelling, polymer erosion, membrane reorganization, solubility change, energy conversion, supply of activation energy for permeation, physical property changes of the materials that comprise the system, or phase transition phenomena, and the like. Examples are presented in J. Heller, Chemically self-regulated drug delivery systems, J. Control. Rel., 8, 111-125 (1988).

[0004] Recently, there has been an increasing interest in developing new protein delivery systems which are both safe and deliver the proteins or peptides in a more controlled manner. Additionally, it has become increasingly desirable to prolong protein delivery over several weeks or even more. Commonly employed pharmaceutical delivery devices include the use of implants, microcapsules, microspheres, and/or nanospheres in the form of nondegradable carriers, biodegradable carriers, or absorbable carriers. Additionally, other microparticle methods of controlled drug release have included the use of micelles, liposomes, etc.

[0005] Nondegradeable carriers include silicone rubber, polyethylene, polymethyl methacrylate(PMMA), polystyrene(PST), ethylene-vinyl acetate copolymer(EVA), polyethylene-maleic anhydride copolymers, polyamides, and others. Though, these carriers may be effective and sometimes useful, the implanted or injected compounds remain in the body as a foreign material after release of the protein and may require a surgical procedure for their removal. Additionally, nondegradeable carriers may also cause certain side effects in the body.

[0006] Conversely, when using biodegradable and/or absorbable carriers, the carrier is gradually degraded or absorbed in the body simultaneously with or subsequent to the protein release. In fact, biodegradable polymers can be designed to degrade in vivo in a controlled manner over a predetermined time period. Suitable biodegradable polymers for use in such sustained release formulations are well described elsewhere and include polyesters such as poly(D,L-lactide), poly(D,L-lactide-co-glycolide), poly(ϵ-caprolactone), poly(hydroxybutylic acid), and poly amino acids, poly(ortho ester)s, polyanhydrides, and poly(alkyl cyanoacrylate)s. These polymers gradually become degraded by enzymatic or non-enzymatic hydrolysis when placed in an aqueous physiological environment. The main mechanism of in vivo degradation for many polymers is hydrolytic degradation in which enzymes may also play a role. Important factors influencing hydrolytic degradation include water permeability, chemical structure, molecular weight, morphology, glass transition temperature, additives, and other environmental factors such as pH, ionic strength, and site of implantation, to name a few.

[0007] Whether microparticles, implants, environment responsive gels, or the like are in the form of nondegradable carriers, biodegradable carriers, or absorbable carriers, a unifying principle among all of these drug delivery mediums is a more prolonged and controlled protein delivery process.

[0008] Various microencapsulation techniques incorporating a protein or peptide into a microparticle carrier are taught in the prior art. However, microparticles having a biodegradable polymer matrix are especially valuable for reasons suggested above. Methods of making biodegradable microparticles include: (a) phase separation by emulsification and subsequent organic solvent evaporation (including complex emulsion methods such as O/W emulsions, W/O emulsions and W/O/W emulsions), (b) coacervation-phase separation, (c) melt dispersion, (d) interfacial deposition, (e) in situ polymerization, (f) spray drying and spray congealing, (g) air suspension coating, and (h) pan coating, to name a few.

[0009] Turning now to biocompatible polymers (including block copolymers, copolymers and the like) capable of existing in a gel state, such polymers are also useful for more prolonged and controlled protein or peptide delivery. In fact, polymers that are sensitive to their environment are especially useful. Environmental conditions that may effect these type of polymers include changes in temperature, pH, ionic strength, solvent, pressure, stress, light intensity, electric field, magnetic field, and/or specific chemical triggers such as glucose. Polymeric gels containing a desired protein or peptide may be administered in a liquid or gel state by a variety of pathways including via parenteral, ocular, topical, transdermal, vaginal, urethral, buccal, transmucosal, pulmonary, transurethral, rectal, intrarespiratory, nasal, oral, aural, sublingual, conjunctival, or by other known methods of administration. Once protein or peptide laden biocompatible and/or biodegradable polymers are administered, the polymer will release the protein or peptide into the body as it biodegrades, is absorbed, or is otherwise reduced to nontoxic products.

[0010] Though the aforementioned methods, i.e., microparticles, implants, and environment responsive gel delivery, have been somewhat effective in controlling protein or peptide delivery in the body, there have also been some limitations with these individual technologies. For example, a known problem with many drug delivery systems involve the effect commonly referred to as burst. Burst occurs as the drug delivery system releases more of a bioactive agent, such as a protein, than is desirable at a given time. The result of burst is that the desired uniform delivery of the protein to the body is undermined. In other words, in some cases,

biodegradable polymers under in vivo conditions can have an initial level of medicament release (or at some other time) which is too high or too low.

[0011] Other limitations include the fact that many biologically active macromolecules, such as proteins and peptides, have low stability. This is particularly true when placed under the harsh fabrication conditions as are present when preparing protein or peptide delivery compositions, e.g., exposure to organic solvents, air-liquid interface, vigorous agitation, sonication, etc. Additionally, many proteins and peptides are highly water soluble.

[0012] In the prior art, attempts have been made to stabilize and/or reduce the solubility of proteins and peptides by complexing the proteins or peptides with multivalent cations such as zinc, calcium, magnesium, copper, ferric iron, and nickel, to name a few. For example, zinc complexed insulin is sparingly water-soluble and may be formulated into long-acting depots. Additionally, as disclosed in U.S. Pat. Nos. 5,912,015 and 5,891,478, human growth hormone (hGH) has been complexed with zinc ion to produce a precipitate. This precipitate has been incorporated into microspheres for a one-month sustained delivery in a biological environment. However, neither of these patents disclose the deposit of proteins or peptides onto biocompatible sparingly soluble particles in order to stabilize and/or prolong the release of proteins from a drug delivery biopolymer. Thus, it would be desirable to provide such a composition so that the solubility of the protein and/or the dissolution rate of protein from a drug delivery biopolymer device are reduced.

SUMMARY OF THE INVENTION

[0013] The present invention is related to compositions and methods for the modulated release of one or more proteins or peptides in a biological environment. Specifically, a drug delivery system for controlled protein release into a biological environment is disclosed comprising a) a sparingly soluble biocompatible particle; b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination. Though the invention merely calls for the depositing of the protein or peptide onto the particle, one mechanism for deposition is preferably adsorption. Others include absorption and coprecipitation.

[0014] By adsorbing the protein or peptide onto the surface of the particle, the protein-particle combination may be incorporated into a long-acting dosage system having a more uniform protein release curve over time than is found in much of the prior art. The present invention also relates to a method for modulating the release of proteins and/or peptides from a biocompatible polymeric matrix.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] In the accompanying drawings which illustrate embodiments of the invention:

[0016] FIGS. **1** is a graphical representation depicting the deposition of hGH onto zinc carbonate as a function of the ratio of zinc carbonate to hGH by weight;

[0017] **FIG. 2** is a graphical representation depicting the deposition of hGH onto zinc D-tartrate as a function of the ratio of zinc D-tartrate to hGH by weight;

[0018] **FIG. 3** is a graphical representation depicting the suppression of hGH release from a gel when deposited on zinc carbonate particles;

[0019] **FIG. 4** is a graphical representation depicting the modulation of insulin release as it relates to the weight ratio between the insulin and zinc carbonate particles; and

[0020] **FIG. 5** is a graphical representation depicting the release of hGH in rats delivered from various compositions, including compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Before the present invention is disclosed and described, it is to be understood that this invention is not limited to the particular process steps and materials disclosed herein as such process steps and materials may vary to some degree. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and is not intended to be limiting as the scope of the present invention will be limited only by the appended claims and equivalents thereof.

[0022] It must be noted that, as used in this specification and the appended claims, singular forms of "a,""an," and "the" include plural referents unless the content clearly dictates otherwise.

[0023] "Biocompatible" shall mean any substance that is not toxic to the body or biological environment. A polymer or polymeric matrix is biocompatible if the polymer, and any degradation products of the polymer, are non-toxic to the recipient or biological environment and also present no significant deleterious effects on the biological environment. A particle is biocompatible if the substance is not toxic to the body or biological environment as the intact particle or as disassociated ions (to extent and at amounts that a sparingly soluble particle may disassociate in a given biological environment).

[0024] "Biodegradable" means that the polymer matrix can break down, degrade, or erode within a biological environment to non-toxic components after or while a protein or peptide has been or is being released to form smaller chemical species by enzymatic, chemical, physical, or other process.

[0025] "Protein" is intended to include one any of a group of complex organic compounds which contain carbon, hydrogen, oxygen, nitrogen, and sometimes sulfur. Specifically included are any combination of insulin, hormones, vaccines, enzymes, antibiotics, antibodies, neuroactive agents, growth factors, cytokines, antigens, glycoproteins, and other known proteins.

[0026] "Biological environment" shall mean any environment, whether in vitro or in vivo, where biological activity may be controlled by protein or peptide release.

[0027] The phrase "effective amount" when referring to the protein shall mean a therapeutically, prophylactically, or diagnostically effective amount which can be determined by a person of ordinary skill in the art. If the biological environment is a warm-blooded animal such as a human, factors to consider include body weight, body surface area, age, physical condition, type of agent or protein used, type

of polymer used, type of particle used, loading dose and subsequent release levels and rates desired.

[0028] "Biocompatible polymeric matrix" or "polymeric matrix" is intended to include any environment responsive polymers or gels (e.g., thermosensitive, pH sensitive, electrical sensitive, etc.), particles, films, pellets, cylinders, discs, implants, microcapsules, microspheres, nanospheres, microparticles, wafers, micelles, liposomes, and other known polymeric configurations used for drug delivery. With respect to forms of microspheres or micro-encapsulation, generally, the diameter is less than about one millimeter and may have a spherical, non-spherical, or irregular shape.

[0029] "Polymeric gel" or "polymer gel" shall mean any polymer, copolymer, block copolymer, and the like that exhibits gelation properties for a period of time when administered within a biological environment, but may be a liquid under conditions not present in that environment.

[0030] "Thermosensitive polymeric gel" shall mean any polymeric gel that, depending on temperature, may exist in liquid state or a gel state, including gels having reverse thermal gelation properties.

[0031] "Surface" when referring to particles is intended to include any surface point on the particle including surface points within pores.

[0032] "Particle" shall mean any substantially insoluble or sparingly soluble particle functional with the present invention. Preferably, the particle is an organic or inorganic salt or oxide particle, though other particles may be functional.

[0033] "Sparingly soluble" or "essentially insoluble" when referring to the particles includes highly insoluble salts and oxides as well as particles that are merely substantially insoluble, so long as the particle is insoluble enough to be functional with the present invention. In other words, particles that exhibit some solubility are included as long as they are functional with the present invention. "Protein-particle combination" shall mean the combination or composite between any protein or peptide that is deposited on a sparingly soluble particle such as a salt or oxide particle. One possible mechanism for deposition is adsorption. Other possible mechanisms include absorption and coprecipitation.

[0034] "Oxide" and "oxides" is intended to specifically include hydroxides as well as oxides that may be used as the particle to which the protein or peptide is deposited.

[0035] "Salt" is intended to include both organic and inorganic salts that may be used as the particle to which the protein or peptide is deposited.

[0036] "Warm-blooded animals," in addition to a generally understood meaning, is intended specifically to also include humans.

[0037] With this in mind, the present invention is drawn toward compositions and methods for delivering proteins from a drug delivery system such that the control of the level of proteins released is enhanced and the period during which controlled release can be maintained is lengthened. The compositions and methods of the present invention provide a needed improvement over the prior art in that the present compositions reduce the dissolution rate of the protein from the drug delivery system and/or the solubility of the desired protein is also greatly reduced.

[0038] Specifically, a drug delivery system for controlled protein release into a biological environment is disclosed comprising a) a sparingly soluble biocompatible particle, including salts and oxides; b) an effective amount of a protein or peptide at least partially deposited onto the particle forming a substantially insoluble protein-particle combination; and c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination.

[0039] A method for controlled delivery of a protein to a warm-blooded animal is also disclosed comprising the steps of a) depositing a protein or peptide onto a sparingly soluble biocompatible particle to form a protein-particle combination; b) loading the protein-particle combination in a biocompatible polymeric matrix; and c) administering the loaded biocompatible polymeric matrix to a warm-blooded animal.

[0040] Additionally, a method of preparing a protein delivery system is disclosed comprising a) depositing a protein or peptide onto a sparingly soluble biocompatible particle to form a protein-particle combination; and b) loading the protein-particle combination into a biocompatible polymeric matrix.

[0041] In any of the compositions and methods of the present invention, the protein-particle combination is preferably prepared at a biocompatible particle to protein or peptide weight ratio from about 1:10 to 100,000:1. Typically, a more practical range of from 1:10 to 1000:1 by weight can be implemented. Additionally, the protein-particle combination should be present in relation to polymeric matrix at from about 0.01 to 30% by weight.

[0042] The drug delivery systems and methods described above require the use of a biocompatible sparingly soluble or essentially insoluble particle for the protein to be deposited onto, preferably by adsorption. Exemplary particles include zinc salts and oxides, magnesium salts and oxides, and calcium salts and oxides, provided the salt is biocompatible and is sparingly soluble or essentially insoluble, though other biocompatible sparingly soluble particles may be used. Specifically, preferred particles include zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, and/or calcium carbonate.

[0043] The proteins or peptides that may be deposited onto the particles of the present invention include, but are not limited to, oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormones (including human, porcine, and bovine), growth hormone releasing factor, insulin, erythropoietin (including all proteins with erythropoietic activity), somatostatin, glucagon, interleukin (which includes IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-

colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins (which includes synthetic analogues and pharmacologically active fragments thereof), enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, and glycoproteins.

[0044] The biocompatible polymeric matrix may come in several configurations within the context of the present invention. For example, the use of environment responsive polymers or gels (e.g., thermosensitive, pH sensitive, electrical sensitive), particles, films, pellets, cylinders, discs, implants, microcapsules, microspheres, nanospheres, microparticles, micelles, and liposomes are exemplary polymeric matrixes that may be used, though other known polymeric configurations may be used. Additionally, the biocompatible polymeric matrix may be in the form of nondegradable polymers, biodegradable polymers, absorbable polymers, and/or bioerodible polymers as are generally known in the art.

[0045] If a biodegradable polymer is used for the polymeric matrix, then poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, polyetheresters, polycaprolactones, polyesteramides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(amino acid)s, poly(alkyl cyanoacrylate)s, and blends and copolymers thereof may be used.

[0046] If a block copolymer is used, then block copolymers including A-B-A block copolymers, B-A-B block copolymers, and/or A-B block copolymers are preferred wherein the A block comprises a hydrophobic polymer and the B block comprises a hydrophilic polymer. Particularly, when using one of the aforementioned block copolymers, the most preferred polymeric matrixes are defined where the A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, polyetheresters, polycaprolactones, polyesteramides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(alkyl cyanoacrylate)s, and blends and copolymers thereof, and the B block is polyethylene glycol or monofunctionally derivatized polyethylene glycol such as methoxy polyethylene glycol. Many of these combinations form acceptable thermal reversible gels.

[0047] If a nondegradable polymer is to be used, then polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, polymethyl methacrylates, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, polyvinyl chlorides, polyvinyl fluorides, poly(vinyl imidazole)s, chlorosulphonate polyolefins, polyethylene oxides, and blends and copolymers thereof are acceptable.

[0048] Further, the polymer or polymeric matrix can include blocked, unblocked, or a blend of blocked and unblocked polymers. A blocked polymer is generally defined as having blocked carboxyl end groups. An unblocked polymer is as classically defined in the art, specifically having free carboxyl end groups.

[0049] Acceptable molecular weights for polymers may be determined by a person of ordinary skill in the art. Factors that may be considered when determining molecular weights include desired polymer degradation rate, mechanical strength, and rate of dissolution of polymer in solvent. Typically, an acceptable range of molecular weights is of about 2,500 Daltons to about 100,000 Daltons, depending upon which polymer is selected for use, among other factors.

[0050] Typically, the compositions and methods of the present invention comprise formulations where a plurality of protein or peptide molecules are present. In such a circumstance, a first portion of the plurality of protein or peptide molecules can be deposited on the particle as part of the protein-particle combination dispersed within the polymeric matrix, and a second portion of the plurality of protein or peptide molecules can be dispersed within the polymeric matrix. Alternatively, multiple types of proteins or peptides can be present as part of a single formulation. For example, a second protein or peptide can be present. In such a circumstance, the second protein or peptide can be deposited on the particle dispersed within the polymeric matrix or be dispersed within the polymeric matrix itself. Typically, the second protein or peptide be present as a plurality of second protein or peptide molecules. Thus, a first portion of the plurality of second protein or peptide molecules can be deposited on the particle as part of a protein-particle combination dispersed within the polymeric matrix, and a second portion of the plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

[0051] The composition of this invention can be administered to any biological environment, whether in vitro or in vivo, where controlled protein delivery is desired. For example, the composition could be administered to a human, or other animal, by injection and/or implantation subcutaneously, intramuscularly, intraperitoneally, intradermally, intravenously, intraarterially, or intrathecally, by administration to mucosal membranes, or by in situ delivery to provide the desired dosage of a biologically active agent based on the known parameters for treatment of the various medical conditions with the protein or peptide.

[0052] Though the compositions are prepared by depositing proteins and/or peptides onto sparing soluble particles, adsorption of the proteins and/or peptides onto a surface of the particle is a preferred method of accomplishing this. Other deposition methods include absorption and coprecipitation techniques, among others. By depositing the proteins onto sparing water-soluble particles, the protein-particle combination can be incorporated into the drug delivery systems of the present invention.

[0053] In U.S. Pat. No. 5,912,015, zinc and magnesium cations were used to modulate the degradation of the polymer matrix and thereby delay the release of biologically active agents, including proteins. However, it was repeatedly stated that the metal cation component must be incorporated separately from the biologically active agent. In the present invention, protein drugs are attached to sparingly soluble particles such as salts or oxides. Therefore, the protein and the sparingly soluble particle are not separate, but physically adjoined. Thus, rather than merely modulating the degrada-

tion of the polymer matrix as has been described in the prior art, the particles are functional with respect to the protein or peptide itself as discussed previously.

[0054] There are several other reasons why the present invention is an improvement over the prior art. First, as discussed, the water solubility of the proteins or peptides is suppressed so that the proteins or peptides may be incorporated into long-acting formulations. Prior to the present invention, proteins and peptides may have been poor candidates for long-acting dosage drug delivery systems due to this limitation. Second, because proteins tend to aggregate and undergo de-amidation or other forms of undesired change in concentrated states, they are difficult to maintain in their useful form for long periods of time. Due to both of these improvements, a single administration may result in long-term release. Third, such a composition lowers or eliminates the initial bursts that generally occur in such a composition. Thus, high initial peaks and other fluctuations of protein release are reduced. As a practical matter, the proteins or peptides deposited onto these water insoluble particles can also enable the proteins to be stored and processed as dry powders, which is a desirable property for pharmaceutical manufacturers. Thus, the protein-containing particle may easily be incorporated into a drug delivery system. Additionally, the rate of drug release from the drug delivery system can also be controlled by selecting appropriate particles, amount of drug deposited, drug loading parameters, polymeric matrixes, particle sizes, etc.

EXAMPLES

[0055] The following examples illustrate the compositions and methods of the present invention. The following examples should not be considered as limitations, but should merely teach how to make the best known drug delivery systems based upon current experimental data.

[0056] Example 1 - Deposition of hGH onto zinc carbonate

[0057] Human growth hormone (hGH) (Humatrope®; 5 mg/bottle) was reconstituted with 3 mL of sterile water for injection. About 100 mg of zinc carbonate particles were added and the suspension was allowed to stand in a refrigerator at 4° C. for about 16 hours. After allowing the particles to settle, HPLC analysis of the supernatant was conducted and no detectable levels of hGH were found. The solid material was collected by centrifugation, washed with deionized water, and dried by lyophilization. HPLC analysis showed that the mass balance recovery of hGH, after removal of zinc using EDTA (50 mM), was quantitative.

[0058] Example 2 - Deposition of hGH onto zinc tartrate

[0059] A similar procedure as described in Example 1 was followed except that about 100 mg of zinc tartrate was added to the hGH solution instead of zinc carbonate. HPLC analysis of the supernatant was conducted and less than 10% of the added hGH was found. The solid material was collected by centrifugation, washed with deionized water, and dried by lyophilization. HPLC analysis showed that the mass balance recovery of the hGH, after removal of zinc using EDTA (50 mM), was quantitative.

[0060] Example 3 - Deposition of insulin onto zinc carbonate

[0061] About 25 mg of zinc insulin was dissolved in about 25 mL of HEPES buffer (10 mM, pH 6). About 100 mg of zinc carbonate was added and the solution was allow to stand in a refrigerator at 4° C. for over 16 hours. HPLC analysis of the supernatant showed that the concentration of insulin was negligible. The solid material was collected and washed with deionized water and the water was removed by lyophilization. HPLC analysis of the solid material showed that the recovery of insulin was quantitative.

[0062] Example 4 - Deposition of hGH onto zinc carbonate

[0063] Several 50 μL aliquots of hGH solution (1.67 mg/mL) were individually placed in 1 mL centrifuge vials. To these solutions, up to 60 μL aliquots of zinc carbonate aqueous suspension (31.54 mg/mL) were added so that the zinc carbonate was present compared to hGH at from 0 to a 22.7:1 ratio by weight. The volume of each vial was adjusted to 110 μL using deionized water. Each mixture was then hand-shaken for 5 minutes and followed by centrifugation. hGH concentration in the supernatant of each was measured by HPLC and the data is shown in **FIG. 1**.

[0064] Specifically, **FIG. 1** depicts the deposition of hGH onto zinc carbonate as a function of the ratio of zinc carbonate to hGH by weight. Essentially complete deposition of hGH onto Zn-carbonate occurred at $ZnCO_3$:hGH weight ratios greater than about 15:1.

[0065] Example 5 - Deposition of hGH onto zinc tartrate

[0066] A similar procedure as described in Example 4 was followed except that zinc tartrate was used in place of zinc carbonate. hGH remaining in solution was analyzed by HPLC. hGH concentration in the supernatant was measured by HPLC and the data is shown in **FIG. 2**.

[0067] As shown, the deposition of hGH onto zinc D-tartrate changes as a function of the ratio of zinc D-tartrate to hGH by weight. Greater than 90% of the hGH was deposited onto the zinc tartrate at Zn-tartrate:hGH weight ratios greater than about 10:1.

[0068] Example 6 - In vitro dissolution of hGH and hGH deposited on zinc carbonate

[0069] hGH/zinc carbonate particles (304 μg of hGH at a 1:20 hGH:$ZnCO_3$ ratio by weight) were placed in a vial and suspended in 100 μL of a thermosensitive tri-block copolymer gel known as ReGel® (20% w/w copolymer in water). ReGel® is biodegradable low molecular weight triblock poly(lactide-co- glycolide) polyethylene glycol copolymer having reverse thermal gelation properties, such as is disclosed in any of U.S. Pat. Nos. 6,201,072, 6,117,949, or 6,004,573. After the gel was set at 37° C., 1 mL of HEPES buffer (10 mM, pH 7.4, containing 0.02% TWEEN-80) was added as the dissolution medium. As a control, this composition was compared to hGH in ReGel® without $ZnCO_3$. Each vial was placed in a 37° C. environment and the entire 1 mL dissolution medium was replaced periodically. hGH in each dissolution medium was measured by HPLC and the data is shown in **FIG. 3**.

[0070] The legend associated with **FIG. 3** is as follows:

[0071] ■=In vitro dissolution (37° C.) of hGH from ReGel® (20% w/w polymer in water) without ZnCO3 into 10 mM Hepes buffer (pH 7.4) containing 0.02% TWEEN-80

[0072] ▲=hGH deposited on zinc carbonate and suspended in ReGel (20% w/w polymer in water) into 10 mM HEPES buffer (pH 7.4) containing 0.02% TWEEN-80

[0073] As shown by the data in **FIG. 3**, hGH release from the gel was significantly suppressed when hGH was deposited on zinc carbonate particles.

[0074] Example 7 - In vitro dissolution of insulin deposited on zinc carbonate

[0075] To 10.22 mL of water was added 32.7 mg of zinc insulin. Complete dissolution was accomplished by addition of 3 drops of acetic acid and allowing the solution to stand in a refrigerator at 4° C. for 16 hours. The solution was then filtered though a 0.2 micron filter. To two 3 mL aliquots of the solution were added 99.5 mg and 30.5 mg of zinc carbonate, respectively. Each mixture was allowed to stand in a refrigerator at 4° C. for about 16 hours. After the suspensions were centrifuged, the insulin levels in each supernatant were found to be negligible by HPLC analysis. The precipitates were washed by deionized water and the water was removed by lyophilization. Solids equivalent to 1 mg of zinc-insulin were placed in 1 mL vials and suspended in 100 μL of a thermosensitive block copolymer gel known as ReGel® (20% w/w copolymer in water). The ReGel® was set in a 37° C. oven and 1 mL of isotonic (NaCl) HEPES buffer solution (10 mM containing 50 mM EDTA, pH 7.4, and 0.02% TWEEN-80) was added as the dissolution medium. Periodically, the entire medium in each solution was replaced by fresh solution. Insulin in each of the dissolution mediums were analyzed by HPLC and the data is presented in **FIG. 4**.

[0076] The legend associated with **FIG. 4** is as follows:

[0077] □–Dissolution of insulin from insulin/$ZnCO_3$ at 1:3 ratio

[0078] ▲=Dissolution of insulin from insulin/$ZnCO_3$ at 1:10 ratio

[0079] As shown by the data of **FIG. 4**, the insulin release was modulated by changing the weight ratio between the insulin and the zinc carbonate.

[0080] Example 8 - In vivo pharmacokinetic studies of hGH sustained release formulations in rats

[0081] Studies were conducted in rats to verify the effect of hGH deposited on sparingly water soluble zinc carbonate salt. Sprague-Dawley rats were given one of five different formulations having various solution bases. Each formulation contained an equivalent of 55 μg of hGH per 0.3 mL of solution. After subcutaneous administration, blood samples (1 mL) were collected at pre-determined intervals for up to 7 days. Plasma was separated and stored at –40° C. before analysis. hGH concentration in each plasma sample was determined by radioimmunoassay (RIA) using kits obtained from DSL Inc. The control used was a product sold under the trademark Humatrope® by Eli Lilly and Company. The data is shown in **FIG. 5**.

[0082] The legend associated with **FIG. 5** is as follows:

■ = Plasma hGH concentration profiles of rats given hGH in diluent
Δ = hGH in 20% ReGel ®
◇ = zinc-hGH complex suspended in 20% ReGel ®
□ = hGH deposited on zinc carbonate particles (hGH:$ZnCO_3$ at a ratio of 1:20 by weight) and suspended in 10 mM HEPES buffer (pH 7.0)
▲ = hGH deposited on zinc carbonate particles at a 1:20 ratio by weight and suspended in 20% ReGel ®

[0083] The data of **FIG. 5** indicates that the release of hGH from ReGel® (20%) alone was nearly identical to the control. Suspending zinc-hGH complex in 20% ReGel® delayed the peak plasma level time (t_{max}) but did not extend the duration substantially. However, depositing hGH onto zinc carbonate at a 1:20 hGH to zinc carbonate ratio, by weight, (without the presence of ReGel®) not only delayed the time (t_{max}), but the peak plasma level (C_{max}) was also significantly reduced. Moreover, incorporating hGH-zinc carbonate particles in ReGel® (20% w/w polymer in water) further reduced the peak plasma level (C_{max}). this data shows the present invention can modulate release of a protein from a polymeric carrier, and illustrates reduced burst effects and extended duration.

[0084] While the invention has been described with reference to certain preferred embodiments, those skilled in the art will appreciate that various modifications, changes, omissions, and substitutions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention be limited only by the scope of the following claims and equivalents thereof.

We claim:

1. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and

c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination.

2. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

3. The drug delivery system of claim 1 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

4. The drug delivery system of claim 1 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

5. The drug delivery system of claim 1 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

6. The drug delivery system of claim 1 wherein said biocompatible particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide,

zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

7. The drug delivery system of claim 1 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

8. The drug delivery system of claim 1 wherein said protein is selected from the group consisting of human growth hormone and insulin.

9. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

10. The drug delivery system of claim 1 wherein said biocompatible polymeric matrix is comprised of a polymer or gel material selected from the group consisting of non-degradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

11. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ϵ-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

12. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ϵ-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

13. The drug delivery system of claim 10 wherein said biocompatible polymeric matrix is comprised of a non-degradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

14. The drug delivery system of claim 1 wherein the protein or peptide is deposited onto a surface of the particle.

15. The drug delivery system of claim 1 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

16. The drug delivery system of claim 1 further comprising a second protein or peptide.

17. The drug delivery system of claim 16 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

18. The drug delivery system of claim 16 wherein the second protein or peptide is dispersed within the polymeric matrix.

19. The drug delivery system of claim 16 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

20. A method for controlled delivery of a protein to a warm-blooded animal comprising:

a) depositing a protein or peptides onto a sparingly soluble biocompatible particle to form a protein-particle combination;

b) loading the protein-particle combination in a biocompatible polymeric matrix; and

c) administering the loaded biocompatible polymeric matrix to a warm-blooded animal.

21. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

22. The method of claim 20 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

23. The method of claim 20 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

24. The method of claim 20 wherein the loaded biocompatible polymeric matrix is delivered by a route selected from the group consisting of parenteral, ocular, topical, implantation, inhalation, vaginal, buccal, transmucosal, transurethral, rectal, nasal, pulmonary, and combinations thereof.

25. The method of claim 24 wherein the route of administration is parenteral.

26. The method of claim 20 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

27. The method of claim 20 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

28. The method of claim 20 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

29. The method of claim 20 wherein said protein is selected from the group consisting of human growth hormone and insulin.

30. The method of claim 20 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

31. The method of claim 20 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

32. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ortho ester)s, poly(ϵ-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

33. The method of claim 31 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, polycaprolactones, poly(ϵ-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

34. The method of claim 31 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

35. The method of claim 20 wherein a plurality of protein or peptide molecules are present, a first portion of said plurality of protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of protein or peptide molecules are dispersed within the polymeric matrix.

36. The method of claim 20 further comprising a second protein or peptide.

37. The method of claim 36 wherein the second protein or peptide is deposited on the particle dispersed within the polymeric matrix.

38. The method of claim 36 wherein the second protein or peptide is dispersed within the polymeric matrix.

39. The method of claim 36 wherein a plurality of second protein or peptide molecules are present, a first portion of said plurality of second protein or peptide molecules are deposited on the particle and dispersed within the polymeric matrix, and a second portion of said plurality of second protein or peptide molecules are dispersed within the polymeric matrix.

40. A method of preparing a protein delivery system comprising:

a) depositing a protein or peptide onto a sparingly soluble biocompatible particle to form a protein-particle combination; and

b) loading the protein-particle combination in a biocompatible polymeric matrix.

41. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight.

42. The method of claim 40 wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 1000:1 by weight.

43. The method of claim 40 wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

44. The method of claim 40 wherein the protein or peptide is deposited onto the particle by a mechanism selected from the group consisting of adsorption, absorption, and coprecipitation.

45. The method of claim 40 wherein the protein or peptide is deposited onto a surface of the particle.

46. The method of claim 40 wherein said biocompatible particle is a sparingly soluble salt or oxide selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, and calcium oxides.

47. The method of claim 40 wherein said sparingly soluble particle is selected from the group consisting of zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium

hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate, calcium carbonate, and combinations thereof.

48. The method of claim 30 wherein said protein or peptide is selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH agonists, growth hormone, growth hormone releasing factor, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-11, IL-12, etc.), interferon-α, interferon-β, interferon-γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies, glycoproteins, and combinations thereof.

49. The method of claim 40 wherein said protein is selected from the group consisting of human growth hormone and insulin.

50. The method of claim 40 wherein said biocompatible polymeric matrix is selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof.

51. The method of claim 40 wherein said biocompatible polymeric matrix is comprised of a polymer material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof.

52. The method of claim 51 wherein said biocompatible polymeric matrix is comprised of a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid) s, polyanhydrides, poly(ortho ester) s, poly(ε-caprolactone), poly(hydroxybutyric acid), polyaminoacids, and blends and copolymers thereof.

53. The method of claim 51 wherein said biocompatible polymeric matrix is a block copolymer selected from the group consisting of A-B-A block copolymers, B-A-B block copolymers, A-B block copolymers, and combinations thereof, and wherein said A block is a biodegradable polymer selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, poly(lactic acid-co-glycolic acid)s, polyanhydrides, poly(ε-caprolactone)s, poly(hydroxybutyric acid)s, poly(aminoacids)s, poly(ortho ester)s, and blends and copolymers thereof, and said B block is polyethylene glycol.

54. The method of claim 51 wherein said biocompatible polymeric matrix is comprised of a nondegradable polymer selected from the group consisting of polyacrylates, polyacrylate esters, silicone rubbers, poloxamers, tetronics, polyethylenes, poly(methyl methacrylate)s, polymethyl methacrylate esters, polystyrenes, ethylene-vinyl acetate copolymers, polyethylene-maleic anhydride copolymers, polyamides, polymers of ethylene-vinyl acetates, acyl substituted cellulose acetates, nondegradable polyurethanes, poly(vinyl chloride)s, poly(vinyl fluoride)s, poly(vinyl imidazole)s, chlorosulphonate polyolefins, poly(ethylene oxide)s, and blends and copolymers thereof.

55. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle selected from the group consisting of zinc salts, zinc oxides, magnesium salts, magnesium oxides, calcium salts, calcium oxides, and combinations thereof;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination, wherein the protein-particle combination has a biocompatible particle to protein or peptide ratio from about 1:10 to 100,000:1 by weight; and

c) a biocompatible polymeric matrix having dispersed therein the protein-particle combination, wherein the protein-particle combination is present in relation to polymeric matrix at from about 0.01 to 30% by weight.

56. A drug delivery system for controlled protein release into a biological environment comprising:

a) a sparingly soluble biocompatible particle;

b) an effective amount of a protein or peptide deposited onto the particle forming a substantially insoluble protein-particle combination; and

c) a biocompatible polymeric matrix said comprised of a polymer or gel material selected from the group consisting of nondegradable polymers, biodegradable polymers, absorbable polymers, bioerodible polymers, block copolymers, and combinations thereof, said polymeric matrix in a form selected from the group consisting of polymeric particles, implants, microcapsules, microspheres, nanospheres, polymeric gels, environment responsive polymers or gels, and combinations thereof, said polymeric matrix having dispersed therein the protein-particle combination.

* * * * *

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(19) **United States**

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Pathak et al. (43) **Pub. Date: Oct. 17, 2002**

(54) **MULTIBLOCK BIODEGRADABLE HYDROGELS FOR DRUG DELIVERY AND TISSUE TREATMENT**

(75) Inventors: **Chandrashekhar P. Pathak**, Austin, TX (US); **Shikha P. Barman**, Bedford, MA (US); **C. Michael Philbrook**, Boston, MA (US); **Amarpreet S. Sawhney**, Lexington, MA (US); **Arthur J. Coury**, Boston, MA (US); **Luis Z. Avila**, Arlington, MA (US); **Mark T. Kieras**, Menlo Park, CA (US)

Correspondence Address:
PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400 (US)

(73) Assignee: **Focal, Inc.**

(21) Appl. No.: **10/114,722**

(22) Filed: **Apr. 2, 2002**

Related U.S. Application Data

(60) Continuation of application No. 09/710,416, filed on Nov. 9, 2000, now Pat. No. 6,410,645, which is a division of application No. 08/692,914, filed on Jul. 26, 1996, now Pat. No. 6,201,065.

(60) Provisional application No. 60/001,723, filed on Jul. 28, 1995.

Publication Classification

(51) **Int. Cl.**[7] **C08L 53/00**

(52) **U.S. Cl.** **525/90**

(57) **ABSTRACT**

Gel-forming macromers including at least four polymeric blocks, at least two of which are hydrophobic and at least one of which is hydrophilic, and including a crosslinkable group are provided. The macromers can be covalently crosslinked to form a gel on a tissue surface in vivo. The gels formed from the macromers have a combination of properties including thermosensitivity and lipophilicity, and are useful in a variety of medical applications including drug delivery and tissue coating.

EXHIBIT E

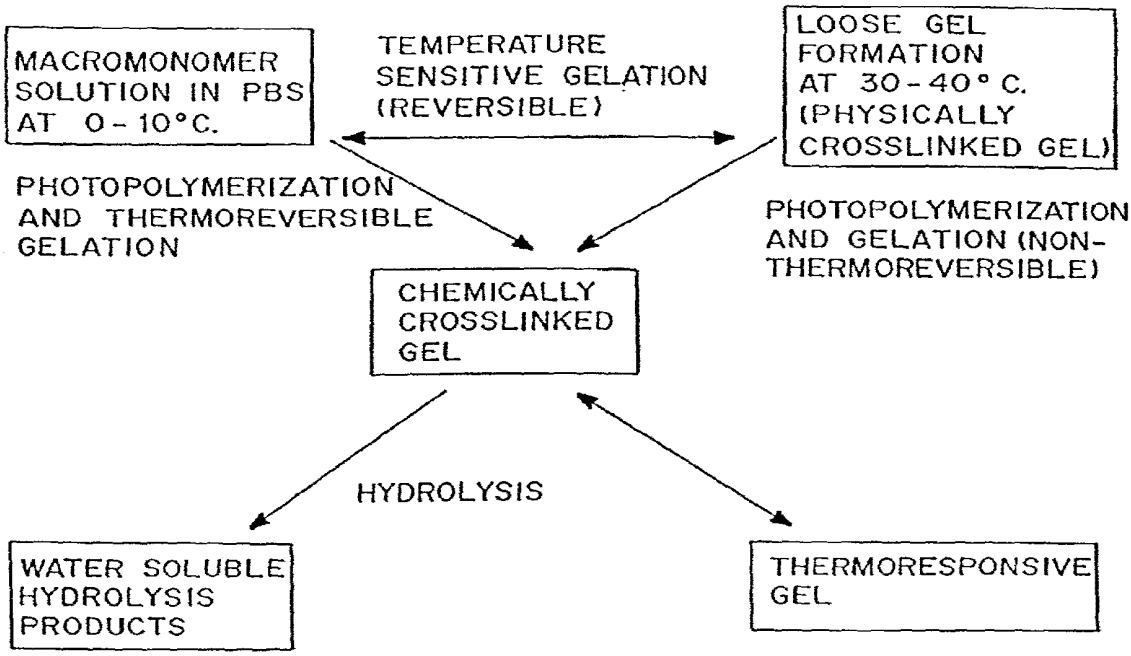

MACROMONOMER SOLUTION IN PBS AT 0-10°C.
TEMPERATURE SENSITIVE GELATION (REVERSIBLE)
LOOSE GEL FORMATION AT 30-40° C. (PHYSICALLY CROSSLINKED GEL)
PHOTOPOLYMERIZATION AND THERMOREVERSIBLE GELATION
PHOTOPOLYMERIZATION AND GELATION (NON-THERMOREVERSIBLE)
CHEMICALLY CROSSLINKED GEL
HYDROLYSIS
WATER SOLUBLE HYDROLYSIS PRODUCTS
THERMORESPONSIVE GEL

FIG. 1

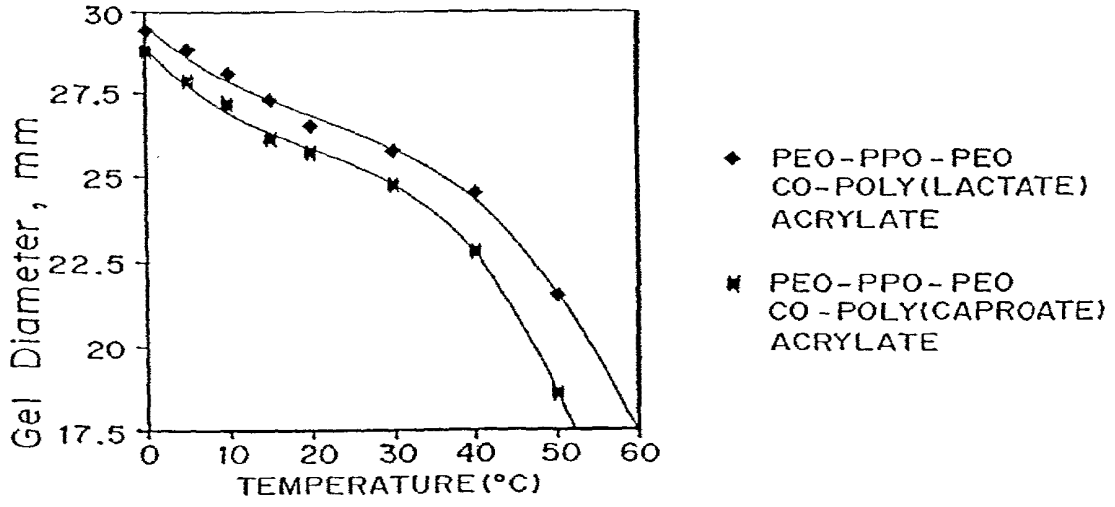

Gel Diameter, mm
30
27.5
25
22.5
20
17.5
0
10
20
30
40
50
60
TEMPERATURE (°C)
PEO-PPO-PEO CO-POLY(LACTATE) ACRYLATE
PEO-PPO-PEO CO-POLY(CAPROATE) ACRYLATE

FIG. 2

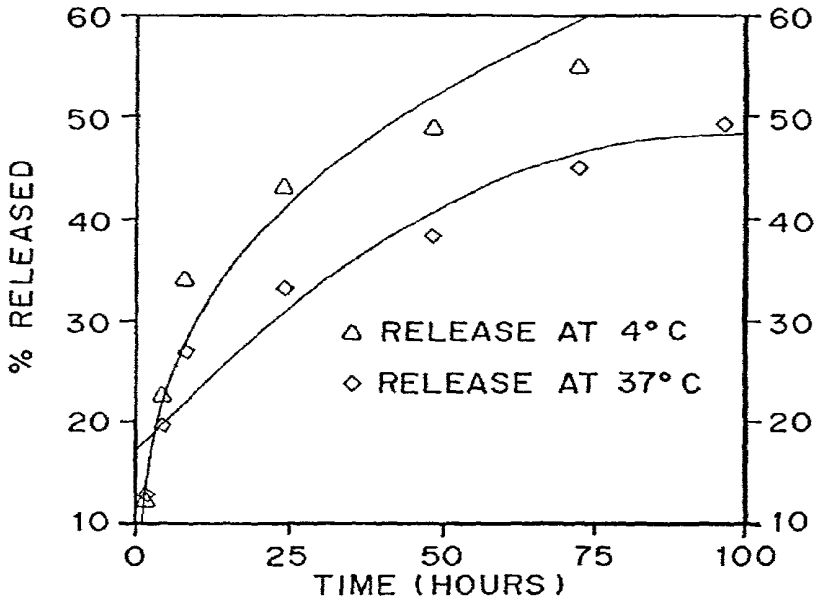

% RELEASED
TIME (HOURS)
RELEASE AT 4° C
RELEASE AT 37° C
60
50
40
30
20
10
0
25
50
75
100

FIG. 3

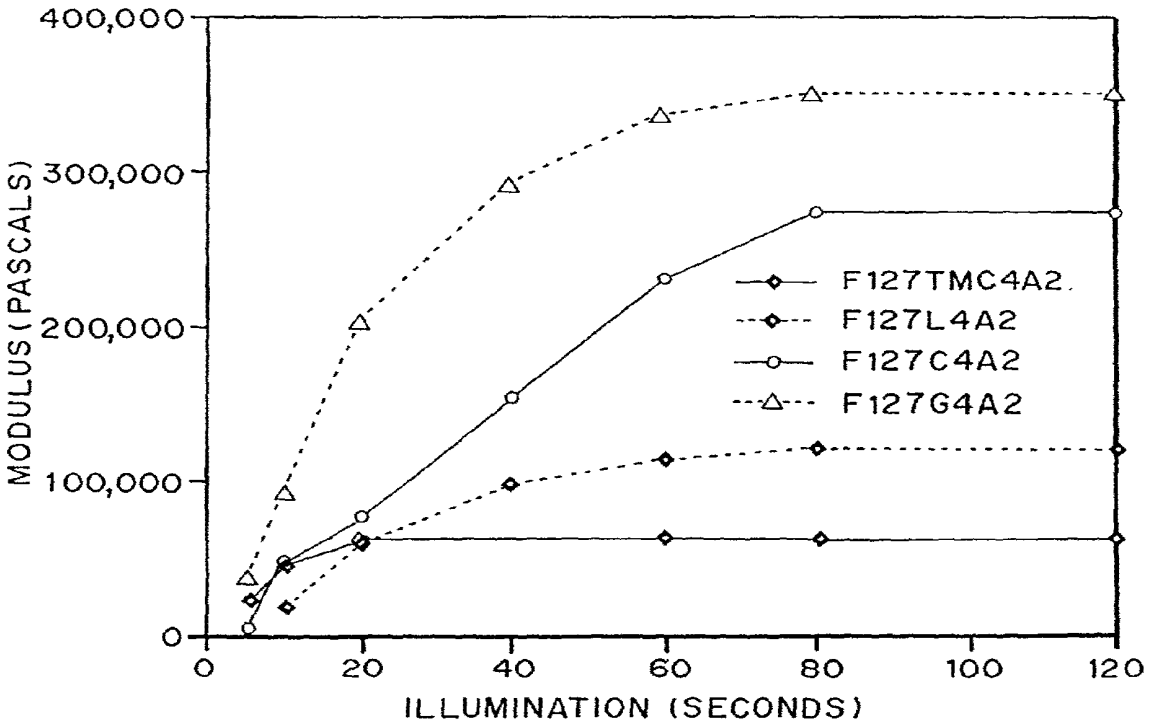

MODULUS (PASCALS)
ILLUMINATION (SECONDS)
F127TMC4A2
F127L4A2
F127C4A2
F127G4A2
400,000
300,000
200,000
100,000
0
0
20
40
60
80
100
120

FIG. 4

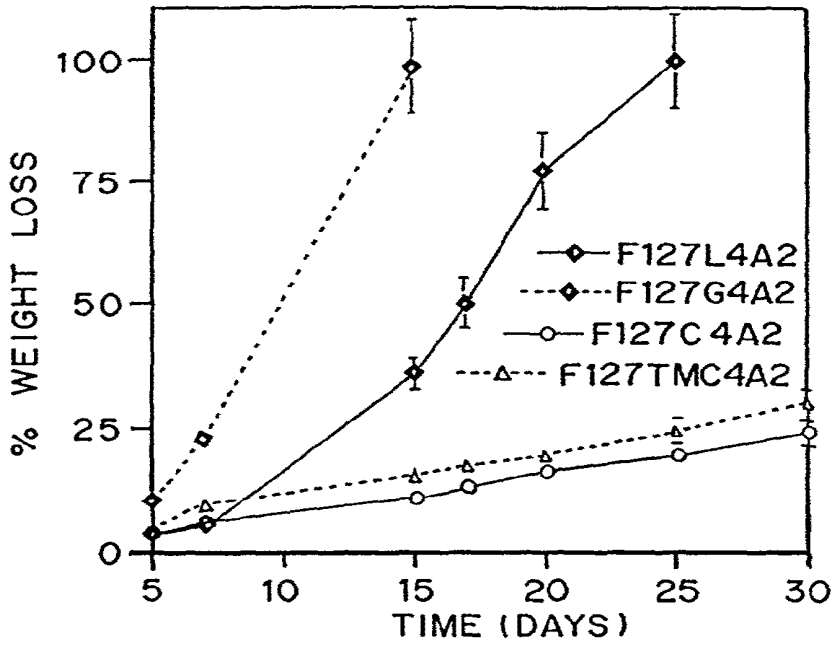

% WEIGHT LOSS
100
75
50
25
0
5
10
15
20
25
30
TIME (DAYS)
F127L4A2
F127G4A2
F127C4A2
F127TMC4A2

FIG. 5

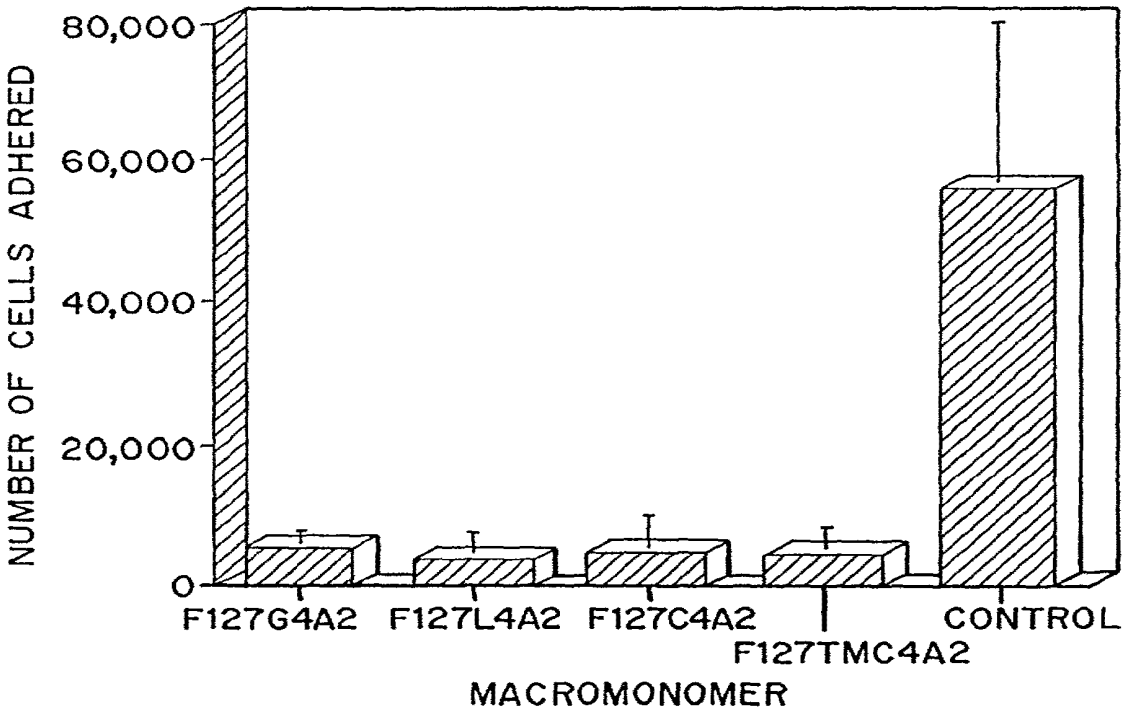

NUMBER OF CELLS ADHERED
80,000
60,000
40,000
20,000
0
F127G4A2
F127L4A2
F127C4A2
F127TMC4A2
CONTROL
MACROMONOMER

FIG. 6

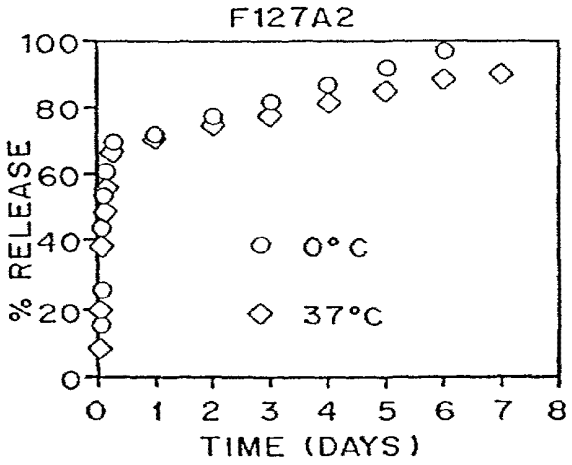


FIG. 7a

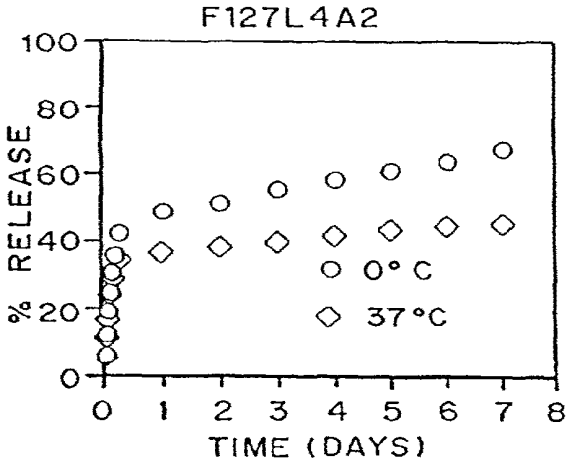


FIG. 7b

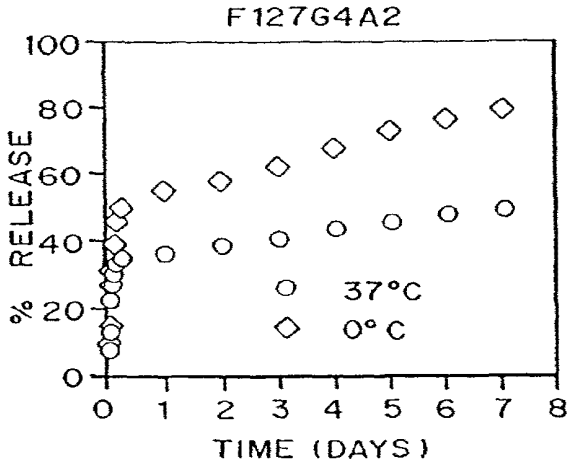


FIG. 7c

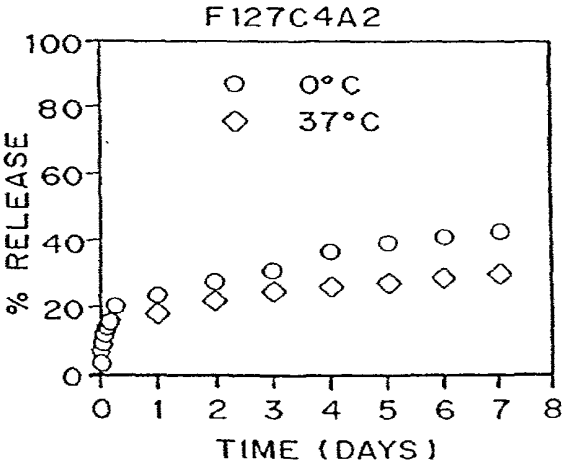


FIG. 7d

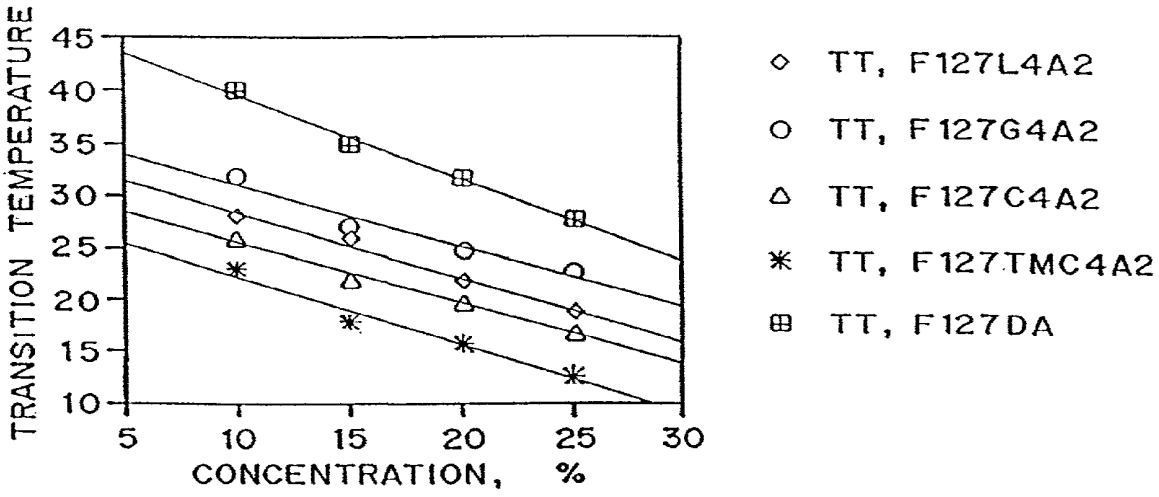

TRANSITION TEMPERATURE
45
40
35
30
25
20
15
10
5
10
15
20
25
30
CONCENTRATION, %
TT, F127L4A2
TT, F127G4A2
TT, F127C4A2
TT, F127TMC4A2
TT, F127DA

FIG. 8a

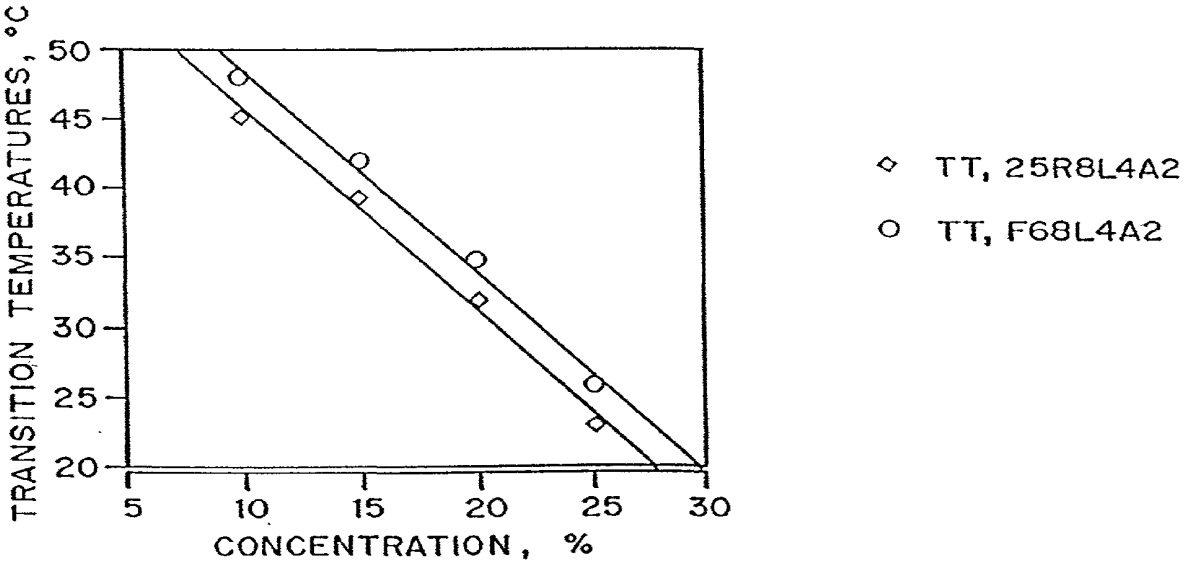
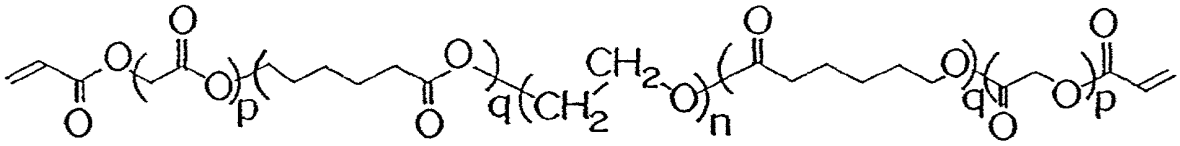

TRANSITION TEMPERATURES, °C
50
45
40
35
30
25
20
5
10
15
20
25
30
CONCENTRATION, %
TT, 25R8L4A2
TT, F68L4A2

FIG. 8b



PEG-Caproate-Glycolate-Acrylate, n = 182
Monomer A: p = 4, q = 1; Monomer B: p = 3, q = 2;
Monomer C: p = 2, q = 3; Monomer D: p = 1, q = 4
p and q are randomly distributed
Structure of macromonomers

FIG. 9

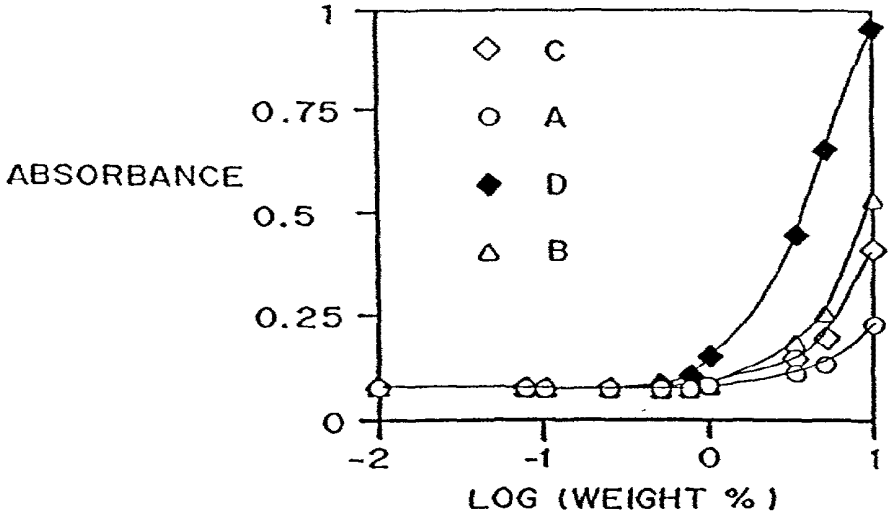


FIG. 10

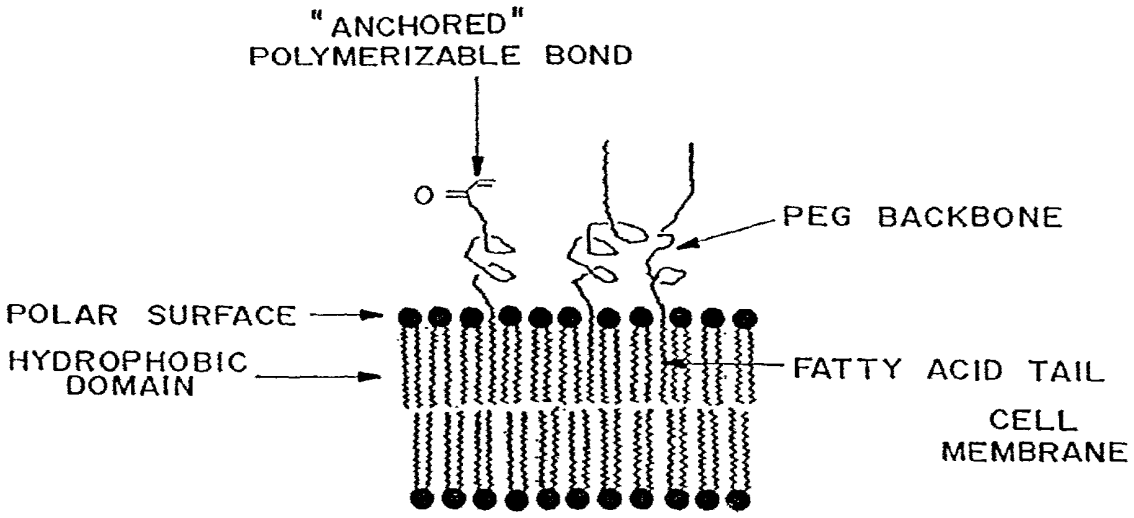


FIG. 11

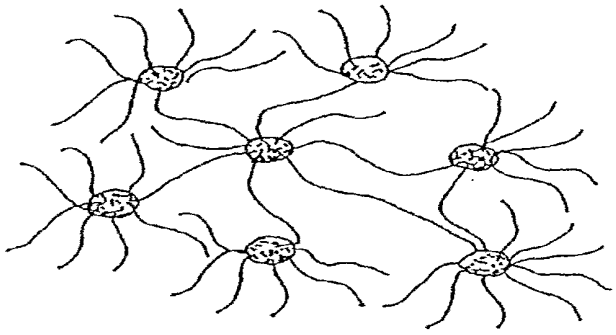


FIG. 12

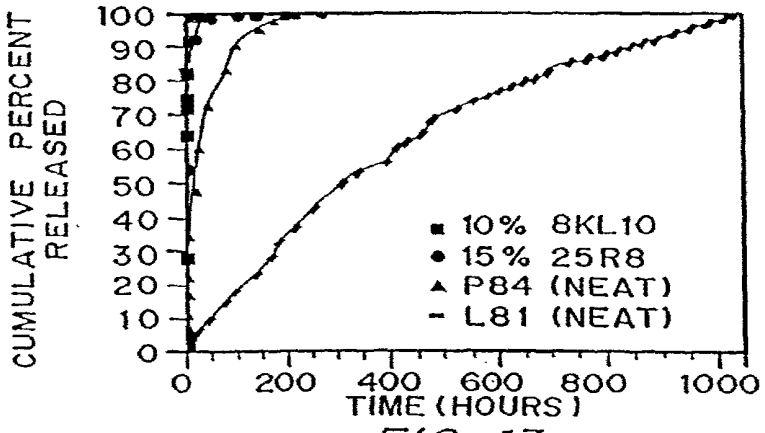


FIG. 13

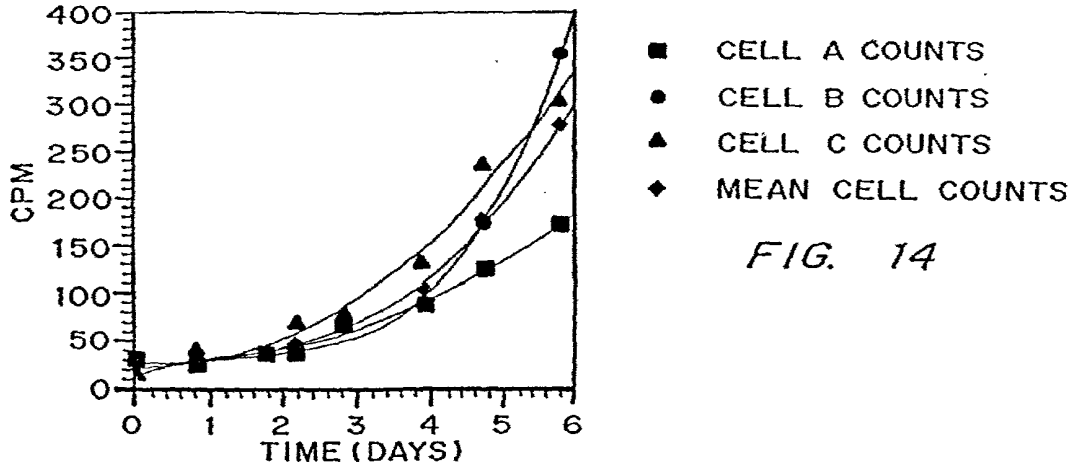


FIG. 14

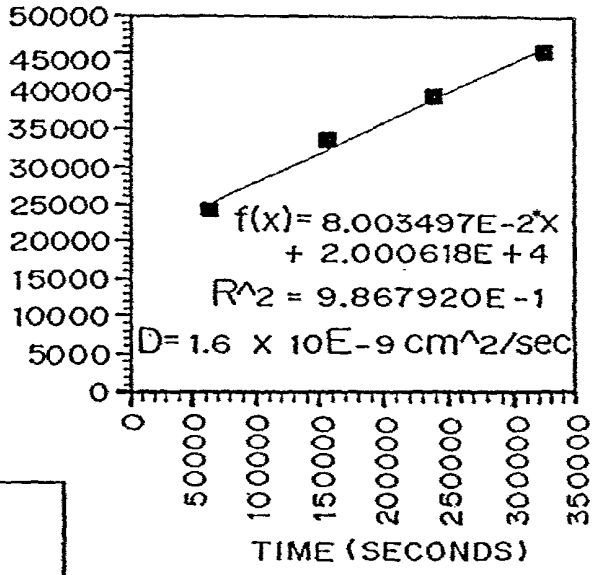


FIG. 15

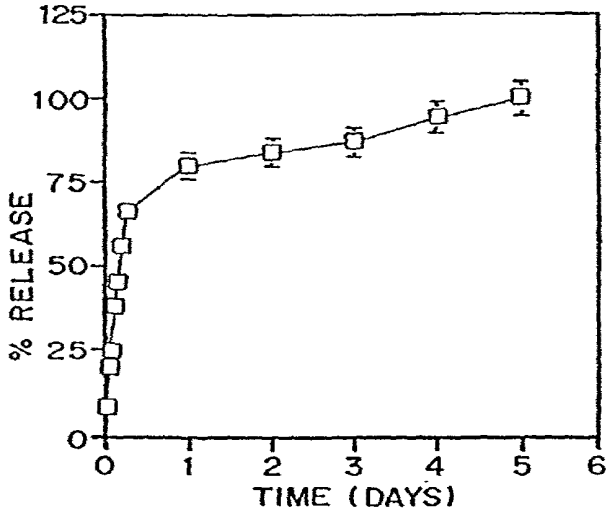


FIG. 16

MULTIBLOCK BIODEGRADABLE HYDROGELS FOR DRUG DELIVERY AND TISSUE TREATMENT

[0001] This application is a continuation-in-part of U.S. Ser. No. 60/001,723, filed Jul. 28, 1995.

BACKGROUND OF THE INVENTION

[0002] The present invention is generally in the area of biodegradable polymers for use in drug delivery and biomedical applications.

[0003] Biodegradable polymers have been developed for use in a variety of surgical and drug delivery applications. The synthesis and biodegradability of poly(lactic acid) was reported by Kulkarni et al., *Arch. Surg.,* 93:839 (1966). Biodegradable polyanhydrides and polyorthoesters having labile backbone linkages have been developed. Domb et al., *Macromolecules,* 22:3200 (1989); and Heller et al, "Biodegradable Polymers as Drug Delivery Systems," Chasin, M. and Langer, R., Eds., Dekker, New York, 121-161 (1990), the disclosures of which are incorporated herein. Polymers which degrade into naturally occurring materials, such as polyaminoacids, also have been developed. Polyesters of α-hydroxy acids, such as lactic acid or glycolic acid, are widely used as biodegradable materials for applications ranging from closure devices, including sutures and staples, to drug delivery systems. Holland et al., *Controlled Release,* 4:155-180, (1986); U.S. Pat. No. 4,741,337 to Smith et al.; and Spilizewski et al., *J. Control. Rel.,* 2:197-203 (1985), the disclosures of which are incorporated herein.

[0004] Degradable polymers containing water-soluble polymer elements have been described. Degradable polymers have been formed by copolymerization of lactide, glycolide, and e-caprolactone with the polyether, polyethylene glycol ("PEG"), to increase the hydrophilicity and degradation rate. Sawhney et al., *J. Biomed. Mater. Res.* 24:1397-1411 (1990). U.S. Pat. No. 4,716,203 to Casey et al. describes the synthesis of a block copolymer of PGA (poly(glycolic acid)) and PEG. U.S. Pat. No. 4,716,203 to Casey et al. describes the synthesis of PGA-PEG diblock copolymers.

[0005] Polymers formed from crosslinkable monomers or prepolymers have been developed in the prior art. Crosslinked hyaluronic acid has been used as a degradable swelling polymer for biomedical applications. U.S. Pat. No. 4,987,744 and 4,957,744 to Della Valle et al.; and Della Valle et al., *Polym. Mater. Sci. Eng.,* 62:731-735 (1991).

[0006] U.S. Pat. No. 5,410,016 to Hubbell et al., the disclosure of which in incorporated herein, discloses the in situ crosslinking of biodegradable, water-soluble macromonomers, ("macromers") to form barrier coatings and matrices for delivery of biologically active agents. Other polymers for drug delivery or other biomedical applications are described in U.S. Pat. No. 4,938,763 to Dunn, U.S. Pat. Nos. 5,160,745 and 4,818,542 to DeLuca, U.S. Pat. No. 5,219,564 to Zalipsky, U.S. Pat. No. 4,826,945 to Cohn, and U.S. Pat. Nos. 5,078,994 and 5,429,826 to Nair, the disclosures of which are incorporated herein by reference. Methods for delivery of the polymers materials include syringes (U.S. Pat. No. 4,938,763 to Dunn et al.) spray applicators (WO 94/21324 by Rowe et al.) and catheter delivery systems (U.S. Pat. Nos. 5,328,471; and 5,213,580 to Slepian). The synthesis of macromers including a central chain of polyethylene glycol, with an oligomeric hydroxyacid at each end and acrylic esters at the ends of the hydroxy acid oligomer also has been reported. Sawhney A. S. et al., *Macromolecules,* 26: 581 (1993); and PCT WO 93/17669 by Hubbell J. A. et al., the disclosures of which are incorporated herein by reference.

[0007] Thermal volume changes in polymeric gels, such as esters and amides of polyacrylic acid, have been described. For example, poly(N-isopropyl acrylamide) based hydrogels, which are thermosensitive in aqueous systems, have been used for controlled drug delivery and other applications. U.S. Pat. No. 5,403,893 to Tanaka et al.; and Hoffman A. S. et al., *J. Controlled Release,* 6:297 (1987), the disclosures of which are incorporated herein. Poly(N-isopropyl acrylamide), however, is non-degradable and is not suitable for applications where biodegradable polymers are required. Non-biodegradable polymeric systems for drug delivery are disadvantageous since they require removal after the drug-polymer device is implanted.

[0008] It is an object of the invention to provide improved polymer systems for use in drug delivery and other biomedical applications such as surgical applications. It is an additional object of the invention to provide polymer systems for use in controlled drug delivery which are capable of releasing a biologically active agent in a predictable and controlled rate. It is a further object of the invention to provide polymers for use in controlled drug delivery which release the active agent locally at a particular targeted site where it is needed. It is another object of the invention to provide polymer systems for use in drug delivery which have properties including volume and drug release which are variable with temperature or other parameters such as pH or ion concentration.

SUMMARY OF THE INVENTION

[0009] Macromers are provided which are capable of gelling in an aqueous solution. In one embodiment, the macromers include at least four polymeric blocks, at least one of which is hydrophilic and at least two of which are hydrophobic, and include a crosslinkable group. The polymer blocks may be selected to provide macromers with different selected properties. The macromers can be covalently crosslinked to form a gel on a tissue surface in vivo. The gels formed from the macromers have a combination of properties including thermosensitivity and lipophilicity, and are useful in a variety of medical applications including drug delivery and tissue coating.

BRIEF DESCRIPTION OF THE FIGURES

[0010] **FIG. 1** is a scheme showing the different gel states and properties of one embodiment of a thermoresponsive biodegradable macromer formed from a polypropylene oxide-polyethylene oxide block copolymer.

[0011] **FIG. 2** is a graph of temperature-dependent changes in gel volume of gels formed by photopolymerization of an acrylated polypropylene oxide-polyethylene oxide block copolymer containing a biodegradable region.

[0012] **FIG. 3** is a graph showing the effects of temperature on dextran release from a gel formed by photopolymerization of an acrylated polypropylene oxide-polyethylene oxide block copolymer.

[0013] **FIG. 4** is a graph illustrating the variation in the speed of photocrosslinking of acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein different biodegradable regions.

[0014] **FIG. 5** is a graph showing the in vitro profiles of degradation rate of gels formed by photocrosslinking of acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein different biodegradable regions.

[0015] **FIG. 6** is a graph illustrating the biocompatibility of gels formed by photocrosslinking acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein different biodegradable regions.

[0016] **FIG. 7** shows graphs illustrating release of fluorescent dextran from gels formed by photocrosslinking acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein biodegradable linkers.

[0017] **FIG. 8** shows graphs of transition temperatures of gels formed from macromers containing biodegradable linkers

[0018] **FIG. 9** illustrates the chemical structures of biodegradable crosslinkable macromers consisting of acrylated poly(propylene oxide)-poly(ethylene oxide) block copolymers having incorporated therein a biodegradable linker.

[0019] **FIG. 10** is a graph of absorbance of a hydrophobic dye vs. log (weight %) of solutions of biodegradable macromers having a hydrophobic region incorporated therein.

[0020] **FIG. 11** is a schematic illustration of a cell membrane including hydrophobic bilayer with a macromer including a hydrophobic tail diffused into the bilayer.

[0021] **FIG. 12** is a schematic illustration of nanospheres or microspheres which can be formed by aggregation and subsequent polymerization of hydrophilic macromers.

[0022] **FIG. 13** is a graph which shows the rate of release of a small drug from gels formed from hydrophobic macromers.

[0023] **FIGS. 14 and 15** are graphs showing diffusivity of a sparingly water soluble drug through a hydrophobic hydrogel.

[0024] **FIG. 16** is a graph showing the release of tetracycline from a hydrogel formed from monomers including a biodegradable region.

DETAILED DESCRIPTION OF THE INVENTION

[0025] Macromers are provided which are crosslinkable to form hydrogels which are useful as matrices for controlled drug delivery. In a preferred embodiment, biodegradable macromers are provided in a pharmaceutically acceptable carrier, and are capable of crosslinking, covalently or non-covalently, to form hydrogels which are thermoresponsive. A biologically active agent may be incorporated within the macromer solution or in the resulting hydrogel after crosslinking. The hydrogels have properties, such as volume and drug release rate, which are dependent upon temperature. The hydrogels may be formed in situ, for example, at a tissue site, and may be used for for controlled delivery of bioactive substances and as tissue coatings. The macromers used to form the hydrogels may be fabricated with domains having specific properties including selected hydrophobicity, hydrophilicity, thermosensitivity or biodegradability, and combinations thereof.

Macromers

[0026] The macro-monomers ("macromers") which are ionically or covalently crosslinkable to form hydrogels preferably consist of a block copolymer. The macromers can be quickly polymerized from aqueous solutions. The macromers are advantageously capable of thermoreversible gelation behavior, and preferably may be polymerized in a solution state or in a gel state. The macromers are defined as including a hydrophilic block capable of absorbing water, and at least one block, distinct from the hydrophilic block, which is sufficiently hydrophobic to precipitate from, or otherwise change phase while within, an aqueous solution, consisting of water, preferably containing salts, buffers, drugs or polymerizing reagents, at temperatures within or near the physiologically compatible range, for example 0 to 65° C. The hydrophilic block optionally may be an amphiphilic block. The macromer may include more than one of the same or different hydrophilic or hydrophobic region. Preferably, the macromers include at least three blocks, or more preferably four blocks.

[0027] The block copolymers may be linear (AB, ABA, ABABA or ABCBA type), star (AnB or BAnC, where B is at least n-valent, and n is 3 to 6) or branched (multiple A's depending from one B). In these formulae, either A or B may be the hydrophilic block, and the other the amphipathic or hydrophilic block, and the additional block C may be either.

[0028] In another embodiment, the macromer includes at least four covalently-linked polymeric blocks, wherein: at least one, or in another embodiment, at least two blocks are hydrophilic, and the hydrophilic blocks individually have a water solubility of at least 1 gram/liter; at least two blocks are sufficiently hydrophobic to aggregate to form micelles in an aqueous continuous phase; and the macromer further includes at least one crosslinkable group. The crosslinkable groups optionally may be separated by at least one degradable linkage capable of degrading under physiological conditions. In one embodiment, at least one hydrophobic block may be separated from any reactive group by at least one hydrophilic block.

[0029] The macromer further may include five total blocks having the same or different properties such as thermal sensitivity, hydrophilicity or hydrophobicity. Each block also may have a combination of properties. For example, a block may be hydrophilic and also thermosensitive. Additionally, the multiblock macromer may include chemically distinct blocks or may incorporate more than one of the same identical block. The macromer is fabricated with a structure and with properties suitable for different applications. For example the macromer may include a central block of dimer fatty acid which includes central hydrocarbon chain of about 30 carbon atoms and two terminal carboxy groups which are esterified with a thermosensitive poloxamer, such as Pluronic L1050. This central molecule further is polylactated at each hydroxy terminus, and end capped with acryloyl chloride. An another embodiment is a poloxamer including polyhydroxy groups polymerized on each end, and wherein

the molecule is end capped at each end with a reactive group such as an acrylate or a secondary isocyanate.

[0030] The configuration of the macromers may be preselected depending on the use of the macromer. The macromers may include at least two hydrophobic blocks, separated by a hydrophilic block. The macromers also may be fabricated with a crosslinkable group which is separated by a degradable group from any other crosslinkable group. One preferred embodiment is wherein the dry macromer absorbs at least about 10% in weight of water. The molecular weight of the macromer preferably is at least 1000 Daltons, or optionally is at least 2000 Daltons, or in an alternative embodiment, at least 4000 Daltons.

[0031] In a preferred embodiment, the macromer includes at least one thermally sensitive region, and an aqueous solution of the macromer is capable of gelling either ionically and/or by covalent crosslinking to produce a hydrogel with a temperature dependent volume. This permits the rate of release of a drug incorporated in the hydrogel to change depending upon the volume of the hydrogel. Useful macromers are those which are, for example, capable of thermoreversible gelation of an aqueous solution of the macromer at a concentration of at least 2% by weight, and wherein the gelation temperature is between about 0° C. and about 65° C. The macromer also may have a phase transition temperature in the range of 0 to 100° C., and wherein the transition temperature is affected by the ionic composition of an aqueous solution of the macromer or the concentration of macromer in the aqueous solution.

[0032] The macromers may be formed by modification of materials and methods described in the prior art. Macromers including a central chain of polyethylene glycol, with oligomeric hydroxy acid at each end and acrylic esters at the ends of the hydroxy acid oligomer are described in Sawhney A. S. et al., *Macromolecules,* 26: 581 (1993); and PCT WO 93/17669 by Hubbell J. A. et al., the disclosures of which are incorporated herein by reference. U.S. Pat. No. 5,410,016 to Hubbell et al., the disclosure of which is incorporated herein by reference, discloses that biodegradable, water-soluble macromers can be crosslinked in situ to form barrier coatings and depots or matrices for delivery of biologically active agents such as therapeutic drugs. In addition to the materials and methods described in U.S. Pat. No. 5,410,016, materials and methods described by Dunn (U.S. Pat. No. 4,938,763), DeLuca (U.S. Pat. Nos. 5,160,745; and 4,818, 542), Zalipsky (U.S. Pat. No. 5,219,564), Cohn (U.S. Pat. No. 4,826,945), Nair (U.S. Pat. Nos. 5,078,994; and 5,429, 826), the disclosures of which are incorporated herein by reference, are useful to form the macromers described herein.

[0033] For example, the macromer may include a poloxamer backbone extended with hydrophobic materials, such as oligolactate moieties, which serve as the biodegradable segment of the molecule, wherein the PEO-PPO-PEO-lactate copolymer is terminated by acrylate moieties. The materials can be combined with, then delivered and photopolymerized in situ, onto target organs to conform to a specific shape.

[0034] The macromers and hydrogels formed therefrom preferably are biocompatible, preferably not causing or enhancing a biological reaction when implanted or otherwise administered within a mammal. The macromers, and any breakdown products of the hydrogels or macromers, preferably are not significantly toxic to living cells, or to organisms. The hydrogels also may have liquid crystalline properties for example at high concentration, which are useful in controlling the rate of drug delivery. Ionic properties can be provided in the backbone of the macromers, conferring the further property of control of delivery and/or physical state by control of the ionic environment, including pH, of the macromer or gel. In one embodiment, the critical ion composition is the hydrogen ion concentration. For example, when a poloxamine, such as a Tetronic surfactant, is used as the core of the macromer, then the resulting macromer has the ionic groups (amines) in the core, and the macromers' ability to gel upon changes in temperature is affected by the pH of the solution.

Thermosensitive Regions

[0035] The macromers may be provided with one or more regions which have properties which are thermoresponsive. As used herein, thermoresponsiveness is defined as including properties of a hydrogel, such as volume, transition from a liquid to a gel, and permeability to biologically active agents, which are dependent upon the temperature of the hydrogel. In one embodiment, the macromers are capable of reversible gelation which is controlled by temperature. The reversible gel further optionally may be crosslinked in situ into an irreversibly and covalently crosslinked gel. This permits the macromer to be applied reliably in surgical applications on a specific area of tissue without running off or being washed off by body fluids prior to gelation or crosslinking.

[0036] In one preferred embodiment, the macromers are capable of gelling thermoreversibly, for example, due to the content of poloxamer regions. Since gelling is thermoreversible, the gel will dissipate on cooling. The macromers may further include crosslinkable groups which permit the gel to be further covalently crosslinked for example by photopolymerization. After crosslinking, the gels are irreversibly crosslinked. However, they retain other significant thermoresponsive properties, such as changes in volume and in permeability.

[0037] By appropriate choice of macromer composition, hydrogels can be created in situ which have thermosensitive properties, including volume changes and drug release which are dependent upon temperature, which can be used to control drug delivery from the hydrogel. Control of drug delivery can be further controlled by adjustment of properties such as hydrophobicity of amphiphilic or other regions in the gel. Change in volume of the hydrogel may readily be measured by examination of macroscopic unrestrained samples during temperature excursions. Changes in excess of 100% in volume may be obtained with hydrogels formed from the macromers, such as an acrylate-capped polyglycolide-derivatized poloxamer of about 30% PPO (polypropylene oxide) content, the expansion occurring gradually on change of the temperature from about 0° C. to body temperature (37° C.). Changes of more than 5% in any linear dimension may be effective in altering the release rate of a macromolecular drug

[0038] The macromers preferably include thermogelling macromers, such as "poloxamers", i.e., poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) ("PEO-

PPO-PEO"), block copolymers. Aqueous polymeric solutions of poloxamers undergo microphase transitions at an upper critical solution temperature, causing a characteristic gel formation. This transition is dependent on concentration and composition of the block copolymer. Alexandridis et al., *Macromolecules,* 27:2414 (1994). The segmental polyether portion of the molecule gives water solubility and thermosensitivity. The material also advantageously have been demonstrated to be biocompatible.

[0039] For example, the macromer may include a poloxamer backbone extended with hydrophobic materials, such as oligolactate moieties, which serve as the biodegradable segment of the molecule, wherein the PEO-PPO-PEO-lactate copolymer is terminated by acrylate moieties. The materials can be combined with a bioactive agent, then delivered and photopolymerized in situ. In addition to poloxamer cores, meroxapols, such as "reversed Pluronics" (PPO-PEO-PPO copolymers) and poloxamines, such as Tetronic™ surfactants, may be used.

[0040] Other polymer blocks which may be provided in the monomer which are capable of temperature dependent volume changes include water soluble blocks such as polyvinyl alcohol, polyvinyl-pyrrolidone, polyacrylic acids, esters and amides, soluble celluloses, peptides and proteins, dextrans and other polysaccharides. Additionally, polymer blocks with an upper critical point may be used, such as other polyalkylene oxides, such as mixed polyalkylene oxides and esters, derivatized celluloses, such as hydroxypropylmethyl cellulose, and natural gums such as konjac glucomannan.

[0041] In another embodiment, the macromer is defined as having an optically anisotropic phase at a concentration at or below the maximal solubility of the macromer in an aqueous solution, at a temperature between about 0 and 65° C.

Crosslinkable Groups

[0042] The macromers preferably include crosslinkable groups which are capable of forming covalent bonds with other compounds while in aqueous solution, which permit crosslinking of the macromers to form a gel, either after, or independently from thermally dependent gellation of the macromer. Chemically or ionically crosslinkable groups known in the art may be provided in the macromers. The crosslinkable groups in one preferred embodiment are polymerizable by photoinitiation by free radical generation, most preferably in the visible or long wavelength ultraviolet radiation. The preferred crosslinkable groups are unsaturated groups including vinyl groups, allyl groups, cinnamates, acrylates, diacrylates, oligoacrylates, methacrylates, dimethacrylates, oligomethoacrylates, or other biologically acceptable photopolymerizable groups.

[0043] Other polymerization chemistries which may be used include, for example, reaction of amines or alcohols with isocyanate or isothiocyanate, or of amines or thiols with aldehydes, epoxides, oxiranes, or cyclic imines; where either the amine or thiol, or the other reactant, or both, may be covalently attached to a macromer. Mixtures of covalent polymerization systems are also contemplated. Sulfonic acid or carboxylic acid groups may be used.

[0044] Preferably, at least a portion of the macromers will have more than one crosslinkable reactive group, to permit formation of a coherent hydrogel after crosslinking of the macromers. Up to 100% of the macromers may have more than one reactive group. Typically, in a synthesis, the percentage will be on the order of 50 to 90%, for example, 75 to 80%. The percentage may be reduced by addition of small co-monomers containing only one active group. A lower limit for crosslinker concentration will depend on the properties of the particular macromer and the total macromer concentration, but will be at least about 3% of the total molar concentration of reactive groups. More preferably, the crosslinker concentration will be at least 10%, with higher concentrations, such as 50% to 90%, being optimal for maximum retardation of many drugs. Optionally, at least part of the crosslinking function may be provided by a low-molecular weight crosslinker. When the drug to be delivered is a macromolecule, higher ranges of polyvalent macromers (ie., having more than one reactive group) are preferred. If the gel is to be biodegradable, as is preferred in most applications, then the crosslinking reactive groups should be separated from each other by biodegradable links. Any linkage known to be biodegradable under in vivo conditions may be suitable, such as a degradable polymer block. The use of ethylenically unsaturated groups, crosslinked by free radical polymerization with chemical and/or photoactive initiators, is preferred as the crosslinkable group.

[0045] The macromer may also include an ionically charged moiety covalently attached to the macromer, which optionally permits gellation or crosslinking of the macromer.

Hydrophobic Regions

[0046] The macromers further may include hydrophobic domains. The hydrophobicity of the gel may be modified to alter drug delivery or three dimensional configuration of the gel. Amphiphilic regions may be provided in the macromers which in aqueous solution tend to aggregate to form micellar domain, with the hydrophobic regions oriented in the interior of these domains (the "core"), while the hydrophilic domains orient on the exterior ("the corona"). These microscopic "cores" can entrap hydrophobic drugs, thus providing microreservoirs for sustained drug release. Kataoka K., et al., *J. Controlled Release,* 24:119 (1993). The fundamental parameter of this supramolecular assemblage of amphiphilic polymers in aqueous solution is the Critical Micellar Concentration (CMC), which can be defined as the lowest concentration at which the dissolved macromolecules begin to self-assemble. By selection of the hydrophilic and other domains, drug delivery can be controlled and enhanced.

[0047] In one embodiment, the macromers are provided with at least one hydrophobic zone, and can form micelles including a region in which hydrophobic materials will tend to bind and thus tend to reduce escape of the drug from the formed gel. The hydrophobic zone may be enhanced by addition of materials, including polymers, which do not contribute to the formation of a gel network but which segregate into such zones to enhance their properties, such as a fatty acid, hydrocarbon, lipid, or a sterol.

[0048] The ability of the macromonomers in one embodiment to form micellar hydrophobic centers not only allows the controlled dissolution of hydrophobic bioactive compounds but also permits the hydrogel to selectively "expand" and "contract" around a transition temperature. This pro-

vides an "on-off" thermocontrol switch which permits the thermally sensitive delivery of drugs.

[0049] The cell membrane is composed of a bilayer with the inner region being hydrophobic. This bilayer is believed to have a fluid and dynamic structure, i.e., hydrophobic molecules can move around in this structure. A hydrophobic tail incorporated in a macromer can diffuse into this lipid bilayer and result in the rest of the macromonomer (thus, the hydrogel) to better adhere to the tissue surface (see **FIG. 11**). The choice of molecular group to be used as hydrophobic tail is guided by the fatty acid composition of the bilayer to assure minimum perturbation of the bilayer structure. Examples of suitable groups are fatty acids, diacylglycerols; molecules from membranes such as phosphatidylserine, and polycyclic hydrocarbons and derivatives, such as cholesterol, cholic acid, steroids and the like. Preferred hydrophobic groups for this purpose are normal constituents of the human body These molecules will be used at a low concentration relative to native molecules in the membrane.

[0050] Use of macromers carrying one or more hydrophobic groups can improve the adherence of a hydrogel to a biological material by anchoring a segment of the hydrogel in the lipid bilayer. This anchoring will cause minimal perturbation to the underlying tissue because the insertion of the fatty acid terminal of the macromer into the lipid membrane involves purely physical interaction. The macromer may be applied by using a prewash of the surface with these molecules, in effect 'preparing' the surface for coupling and/or an in situ photopolymerization of a mixture of these lipid-penetrating molecules with the crosslinkable macromers.

[0051] The hydrophobic region may include oligomers of hydroxy acids such as lactic acid or glycolic acid, or oligomers of caprolactone, amino acids, anhydrides, orthoesters, phosphazenes, phosphates, polyhydroxy acids or copolymers of these subunits. Additionally the hydrophobic region may be formed of poly(propylene oxide), poly(butylene oxide), or a hydrophobic non-block mixed poly(alkylene oxide) or copolymers thereof. Biodegradable hydrophobic polyanhydrides are disclosed in, for example, U.S. Pat. Nos. 4,757,128, 4,857,311, 4,888,176, and 4,789,724, the disclosure of which is incorporated by reference herein. Poly L-lactide, or poly D,L-lactide for example may be used. In another embodiment the hydrophobic region may be a polyester which is a copolymer of poly(lactic-co-glycolic) acid (PLGA).

[0052] The macromer also may be provided as a mixture including a hydrophobic material non-covalently associated with the macromer, wherein the hydrophobic material is, for example, a hydrocarbon, a lipid, a fatty acid, or a sterol.

Hydrophilic Regions.

[0053] Water soluble hydrophilic oligomers available in the art may be incorporated into the biodegradable macromers. The hydrophilic region can be for example, polymer blocks of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), or polysaccharides or carbohydrates such as hyaluronic acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, or proteins such as gelatin, collagen, albumin, ovalbumin, or polyamino acids

Biodegradable Regions

[0054] Biodegradable molecules or polymers thereof available in the art may be incorporated into the macromers. The biodegradable region is preferably hydrolyzable under in vivo conditions. In some embodiments, the different properties, such as biodegradability and hydrophobicity or hydrophilicity, may be present within the same region of the macromer.

[0055] Useful hydrolyzable groups include polymers and oligomers of glycolide, lactide, epsilon-caprolactone, other hydroxy acids, and other biologically degradable polymers that yield materials that are non-toxic or present as normal metabolites in the body. Preferred poly(alpha-hydroxy acids) are poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid). Other useful materials include poly(amino acids), polycarbonates, poly(anhydrides), poly(orthoesters), poly(phosphazines) and poly(phosphoesters). Polylactones such as poly(epsilon-caprolactone), poly(delta-caprolactone), poly(delta-valerolactone) and poly(gamma-butyrolactone), for example, are also useful. The biodegradable regions may have a degree of polymerization ranging from one up to values that would yield a product that was not substantially water soluble. Thus, monomeric, dimeric, trimeric, oligomeric, and polymeric regions may be used.

[0056] Biodegradable regions can be constructed from polymers or monomers using linkages susceptible to biodegradation, such as ester, peptide, anhydride, orthoester, phosphazine and phosphoester bonds. The time required for a polymer to degrade can be tailored by selecting appropriate monomers. Differences in crystallinity also alter degradation rates. For relatively hydrophobic polymers, actual mass loss only begins when the oligomeric fragments are small enough to be water soluble. Thus, initial polymer molecular weight influences the degradation rate.

Therapeutic Applications

[0057] Biodegradable, temperature responsive hydrogels can be formed in situ and may be use in a variety of therapeutic applications including surgical applications. In one embodiment the gels can be applied topically to the skin to treat a variety of conditions such as abrasion, keratoses, inflammatory dermatoses, injury resulting from a surgical procedure, and disturbed keratinization. The hydrogels may include therapeutic agents such as antibiotics, or antifungals for the localized treatment of different skin conditions.

[0058] Macromers which are liquid at room temperature and gel at body temperature, such as macromers including a Pluronic™ poloxamer, may be used in treatment of burns and other external injuries. The hydrogels are useful in burn applications, since the hydrogel layer formed on the skin provides local or transdermal delivery of drug to the burn site; maintains high moisture levels on severely burned sites, thus diminishing dehydration; adheres strongly to the damaged tissue, and is elastic, thus minimizing delamination and "peeling" of the hydrogel dressing; and absorbs exudate from the wound. Hydrogels may be selected which dissolve into components which are absorbable and non-toxic, which promote healing, and gel spontaneously and quickly on the burn site, prior to optional further crosslinking.

[0059] The macromers also may be applied to biological tissue, or on the surface of a medical device, to form

hydrogels in a variety of surgical applications for the treatment of tissue or organs. The gel also may be applied between two surfaces, such as tissue surfaces, to adhere the surfaces. The hydrogels may be applied to tissue such as vascular tissue, for example for the treatment of restenosis of the arteries or in angioplasty procedures. A biologically active material may be provided in the gel optionally in the form of particles, microparticles, prodrug conjugates, or liposomes. The macromers may be designed such that the crosslinked gel changes in permeability in response to a change in temperature, ionic concentration or a change in pH, thereby altering the rate of drug release from the hydrogel.

Drug Delivery

[0060] The macromers may be crosslinked reversibly or irreversibly to form gels for controlled drug delivery applications. The composition and properties of the macromers can be selected and fabricated to produce hydrogels with desired drug delivery properties. The drug may be provided in the macromer solution prior to or after administration, and either before or after gel formation, depending on the macromer composition.

[0061] For example, the gels can be designed to have a selected rate of drug release, such as first order or zero order drug release kinetics. For specific drugs, such as peptides, the composition of the gel may be designed to result in pulsatile or mixed wave release characteristics in order to obtain maximum drug efficacy and to minimize side effects and tolerance development. Bae et al., *Pharmaceutical Research,* 8: 531 (1991).

[0062] The drug release profiles can be selected by the use of macromers and gels formed therefrom that respond to specific external stimuli such as ultrasound, temperature, pH or electric current. For example, the extent of swelling and size of these hydrogels can be modulated. Changes induced in the swelling directly correlate to the rate of release of the incorporated drugs. Through this, a particular release profile may be obtained. The hydrogels are preferably biodegradable so that removal is not required after administration or implantation.

[0063] The gels permit controlled drug delivery and release of a biologically active agent in a predictable and controlled manner locally at the targeted site where it is needed, when the tissue to be treated is localized. In other embodiments, the gels also can be used for systemic delivery.

[0064] A variety of therapeutic agents can be delivered using the hydrogels. Examples include synthetic inorganic and organic compounds, proteins and peptides, polysaccharides and other sugars, lipids, gangliosides, and nucleic acid sequences having therapeutic, prophylactic or diagnostic activities. Nucleic acid sequences include genes, antisense molecules which bind to complementary DNA to inhibit transcription, and ribozymes. The agents to be incorporated can have a variety of biological activities, such as vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, antibiotics, antivirals, antisense, antigens, and antibodies. Proteins including antibodies or antigens can also be delivered. Proteins are defmed as consisting of 100 amino acid residues or more; peptides are less than 100 amino acid residues. Unless otherwise stated, the term protein refers to both proteins and peptides. Examples include insulin and other hormones.

[0065] Specific materials include antibiotics, antivirals, antiinflammatories, both steroidal and non-steroidal, antineoplastics, anti-spasmodics including channel blockers, modulators of cell-extracellular matrix interactions including cell growth inhibitors and anti-adhesion molecules, enzymes and enzyme inhibitors, anticoagulants and/or antithrombotic agents, growth factors, DNA, RNA, inhibitors of DNA, RNA or protein synthesis, compounds modulating cell migration, proliferation and/or growth, vasodilating agents, and other drugs commonly used for the treatment of injury to tissue. Specific examples of these compounds include angiotensin converting enzyme inhibitors, prostacyclin, heparin, salicylates, nitrates, calcium channel blocking drugs, streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), colchicine and alkylating agents, and aptomers. Specific examples of modulators of cell interactions include interleukins, platelet derived growth factor, acidic and basic fibroblast growth factor (FGF), transformation growth factor β (TGF β), epidermal growth factor (EGF), insulin-like growth factor, and antibodies thereto. Specific examples of nucleic acids include genes and cDNAs encoding proteins, expression vectors, antisense and other oligonucleotides such as ribozymes which can be used to regulate or prevent gene expression. Specific examples of other bioactive agents include modified extracellular matrix components or their receptors, and lipid and cholesterol sequestrants.

[0066] Examples of proteins further include cytokines such as interferons and interleukins, poetins, and colony-stimulating factors. Carbohydrates include Sialyl lewis^x which has been shown to bind to receptors for selectins to inhibit inflammation. A "Deliverable growth factor equivalent" (abbreviated DGFE), a growth factor for a cell or tissue, may be used, which is broadly construed as including growth factors, cytokines, interferons, interleukins, proteins, colony-stimulating factors, gibberellins, auxins, and vitamins; further including peptide fragments or other active fragments of the above; and further including vectors, i.e., nucleic acid constructs capable of synthesizing such factors in the target cells, whether by transformation or transient expression; and further including effectors which stimulate or depress the synthesis of such factors in the tissue, including natural signal molecules, antisense and triplex nucleic acids, and the like. Exemplary DGFE's are vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), basic fibroblast growth factor (bFGF), bone morphogenetic protein (BMP), and platelet derived growth factor (PDGF), and DNA's encoding for them. Exemplary clot dissolving agents are tissue plasminogen activator, streptokinase, urokinase and heparin.

[0067] Drugs having antioxidant activity (i.e., destroying or preventing formation of active oxygen) may be provided in the hydrogel, which are useful, for example, in the prevention of adhesions. Examples include superoxide dismutase, or other protein drugs include catalases, peroxidases and general oxidases or oxidative enzymes such as cytochrome P450, glutathione peroxidase, and other native or denatured hemoproteins.

[0068] Mammalian stress response proteins or heat shock proteins, such as heat shock protein 70 (hsp 70) and hsp 90, or those stimuli which act to inhibit or reduce stress response proteins or heat shock protein expression, for example, flavonoids, may be provided in the hydrogel.

[0069] The macromers may be provided in pharmaceutical acceptable carriers known to those skilled in the art, such as saline or phosphate buffered saline. For example, suitable carriers for parenteral adminstration may be used.

Administration of Macromers

[0070] Modern surgical procedures which provide access to a variety of organs using minimally invasive surgical devices may be used to apply the macromers. Using techniques such as laparoscopy/endoscopy, it is possible to deposit a macromonomer solution at a localized site and subsequently polymerize it inside the body. This method of "on-site" polymerization offers unique advantages such as conformity to specific organs and adherence to underlying tissue. Hill-West J. L. et al., *Obstetrics & Gynecology,* 83:59 (1994). Catheter delivery systems available in the art also may be used as described, for example, in U.S. Pat. Nos. 5,328,471 and 5,213,580 to Slepian. The macromer also may applied during surgery conducted through the cannula of a trocar.

Formation of Microspheres

[0071] In one embodiment, the biodegrabable macromers are crosslinked, either reversibly or nonreversibly to form microspheres. As used herein, the term "microspheres" includes includes particles having a uniform spherical shape or an irregular shape, and microcapsules (having a core and an outer layer of polymer) which generally have a diameter from the nanometer range up to about 5 mm. In a preferred embodiment, the microspheres are dispersed in biocompatible, biodegradable hydrogel matrices. The microspheres are useful for controlled release and targeted delivery of drugs within the body.

[0072] The microspheres are formed in one embodiment by aggregation and subsequent polymerization of portions of the macromers which are similar in charge properties such as hydrophilicity. This results in a matrix which consists of spontaneously-assembled "nodes", which may be crosslinked covalently, and may be further covalently linked to hydrophilic bridges of the macromers to form a hydrogel.

[0073] When the macromer is amphiphilic and includes hydrophobic and hydrophilic domains, in an aqueous environment, at or above a certain concentration, the molecules to arrange themselves into organized structures called micelles, at the critical micellar concentration (CMC). These micelles can be of different shapes and sizes, though are generally spherical or elliptical shape. When the solution is water, the hydrophobic portions are at the center of the micelle while the hydrophilic tails orient themselves toward water. The interior core of a typical surfactant has a size from 10-30 Angstroms. Pluronic™ poloxamer based biodegradable macromers, as described in Example, undergo micellization in an aqueous environment with CMC values ranging between 0 and 5% (w/v). After photopolymerization and gelation, this micellar structure is preserved in the crosslinked gel. On a microscopic level, the gel contains micelles which are interconnected by covalent bonds to form the gel. These micellar domains or microspheres can be used for the controlled or sustained release of drugs. A schematic representation of such a material is shown in **FIG. 12**. Controlled, pseudo-zero order release of small compounds such as chlorohexidine is possible from such hydrogels.

[0074] The hydrogel thus is formed in one embodiment by providing a solution of macromer in aqueous solution (with or without drug); "freezing" the micellar structure of the macromer by a chemical crosslinking via a chemical reaction; adding the drug to the crosslinked macromer if it has not been already added; and using the resultant dispersed composite, containing microspheres consisting of drug-attracting micellar cores, for drug delivery.

[0075] In addition to photopolymerization, crosslinking can be implemented by, for example, isocyanate-amine chemistry, or hydroxy- or aldehyde-amine chemistry, to freeze micellar structure. For example, isocyanate terminated poloxamer lactate diol can react in water to form crosslinked polyurethane based networks. This is an advantageous method of forming a drug delivery device for local or systemic delivery, because the formation of the delivery-controlling micropheres and the microsphere-confining gel is accomplished simultaneously, and may be accomplished at the site of delivery in a few seconds by photopolymerization.

[0076] In one embodiment the macromer includes PEO segments, and hydrophobic "ends" containing reactive groups, and the micellar domains are hydrophobic and are interlinked by the PEG segments to form a hydrogel. Reversible gelling microsphere-forming macromers also may be made from Pluronics™ (PEG-PPO-PEG), lactylated and acrylate-capped, which are gelled and reacted in a non-aqueous phase. A hydrophilic drug then may be added (while in the hydrophobic solvent) which partitions to the hydrophilic core. Because the micelles have been crosslinked in the hydrophobic environment, they will not be able to revert to the conformation which they would normally assume in a hydrophilic environment. The trapped hydrophilic drug molecules then need to diffuse through a relatively hydrophobic region to escape from the nanoparticle. This permits flexibility in the formation of microspheres.

[0077] They may be hydrophilic or hydrophobic depending on the solvent in which they are polymerized, and on the composition of the macromers.

[0078] In other embodiments, physical or chemical crosslinking to form hydrogels (or organogels) can occur in zones other than those responsible for the primary sustained release characteristics of the matrix. For example, "single-ended" materials could have alternative reaction sites on the non-micellar ends, which could subsequently reacted to form a gel. Since matrix-controlled drug delivery is a function of both diffusion from the micelles and of matrix degradation, manipulation of the macromolecular backbone can also control matrix degradation. This can occur through stabilization of hydrolytic groups by their chemical and physical environment (for example, macromers based on reverse Pluronic™ gels are more stable than normal Pluronic™ gels, in aqueous solution). It is possible that the increased hydrophobicity of the environment of the lactide ester bonds, due to the adjacent block being PPO rather than PEO, inhibits hydrolysis of the bond.

[0079] Alternatively, and particularly in gel-forming compositions, the cross-linking reactive groups or biodegradable

groups may be in the hydrophilic portions of the macromers, so that the hydrophobic domains would not be locally crosslinked in the hydrophobic regions, while the micelles would still be stabilized by the crosslinking of the material, and particular hydrophobic sections of macromers would be sterically restricted to one or only a few different micelles. In either of these cases, the hydrophobic zones are not rigidly crosslinked, but are connected to crosslinks via the hydrophilic blocks, which may be very flexible. The hydrophobic blocks thus can associate above or below a critical temperature, and dissociate on change in temperature. This allows, for example, both thermosensitive gelation and thermosensitive variation in drug diffusion rate.

[0080] The hydrogels may be designed to be biodegradable by incorporation of a group such as a lactide, glycolide or other self-degrading linkage. Alternatively, this is not necessary when non-gelled nanospheres are formed, since these are small enough to be removed by phagocytosis. Control of the rates of delivery of both small and large molecules can be obtained by control of the hydrophobicity of the associating hydrophobic domains of amphipathic hydrogels.

[0081] The crosslinked microspheres containing a biologically active agent, in either gel or dispersion form, can be made in a single step. In addition to drug delivery applications, the method is suitable for non-medical uses including delivery of agricultural materials such as herbicides and pesticides and in water treatment.

[0082] The present invention will be further understood by reference to the following non-limiting examples.

EXAMPLE 1

Synthesis and Thermal Responsiveness of F127-(Lactate)6-Acrylate

[0083] a) Synthesis

[0084] F127-actate)0-(lacrylate (unlactated control) (=F127A2?) was synthesized by acrylating 100 g of Pluronic™ F127 (polypropylene oxide-polyethylene oxide block copolymer, BASF, mol. wt. 12000) ("F127") in anhydrous toluene using triethylamine and acryloyl chloride, in an argon atmosphere at 60° C. for 10 minutes. The hot, turbid reaction mixture was filtered and the filtrate was added to a large excess of hexane. The monomer was collected by vacuum filtration and dried in vacuum to a constant weight.

[0085] F127-(lactate)6-acrylate was synthesized as follows F127 was melt dried in vacuo at 100° C. for 4 hours. D,L-lactide (Boehringer Ingelheim) was added to the melt under a nitrogen flush, followed by stannous octoate as a ring opening catalyst. After a reaction time of 4 hours, the melt was dissolved in toluene and precipitated in a large excess of hexane. Acrylation of F127-(lactate)6 was carried out as described above for the acrylation of F127-(lactate)0-acrylate. All macromonomers were characterized by NMR and HPLC.

[0086] The relationship between the macromer, the thermally-reversible (physical) gel, and the irreversible (crosslinked) gel is shown in **FIG. 1**.

[0087] b) Measurement of the Sol-gel Transition as a Function of Concentration and Temperature

[0088] Thermoreversible gel formation of the aqueous solutions of the macromonomers at a certain transition temperature was demonstrated. This transition temperature was recorded as a function of temperature and concentration. The results demonstrated that sol-gel transition can be controlled through the incorporation of hydrophobic lactyl units.

[0089] Transition temperature as a function of concentration was determined by preparing 20% w/v aqueous solutions of F127-(lactate)0-acrylate and F127-(lactate)6-acrylate as stock solutions. 15 % (w/v), 12.5% (w/v), 10% (w/v) and 5% (w/v) macromonomer aqueous? solutions in screw cap vials were prepared by dilutions of the stock solutions. The solutions were allowed to equilibrate at 25° C. The vials were inverted and observed for fluid flow. The concentration at which no fluid flow was observed was recorded (see Table 1).

[0090] The transition temperature as a function of temperature was determined by preparing 10% (w/v) aqueous solutions of F127-(lactate)6-acrylate and F127-(lactate)0-acrylate and equilibrating them at room temperature. (The concentration of the solutions are wt/vol % in aqueous solution unless otherwise stated.) The sample vials were immersed in a temperature controlled bath and the fluid flow was observed at different temperatures. The temperature at which no fluid flow was observed was recorded (see Table 1).

TABLE 1

Macromonomers	Sol-GeL Transition (% w/v)**	Sol-Gel Transition (° C.)***
F127-(Lactate)0-Acrylate	30	40
F127-(Lactate)6-Acrylate	10	25

**Sol-Gel Transition as a function of concentration (temperature 25° C.).
***Sol-Gel Transition of 10% w/v solutions as a function of temperature.

[0091] c) Polymerization and Measurement of Hydrogel Dimensions

[0092] A 10% solution of F127-(lactate)6-acrylate in PBS (phosphate buffered saline) was polymerized using long wave UV light. The polymerizations were performed in a cylindrical plastic mold. Darocur™ 2959 (Ciba Geigy) was used as the photoinitiator. The hydrogel was allowed to reach equilibrium swelling by immersing in PBS for 24 hours at ambient temperature. The change in dimension of the hydrogel at temperatures ranging from 0-50° C. was measured using vernier calipers, and is shown in **FIG. 2**. At low temperatures, the hydrophobic PPO (polypropylene oxide) segments of the hydrogel may dissolve and swell, and increase the dimensions of the gel. At high temperatures, the PPO segments may become hydrophobic and collapse into micromicellar hydrophobic domains, which exclude water resulting in reduced swelling and smaller dimensions.

[0093] d) Degradation Experiments

[0094] Hydrogels were prepared using 10% macromonomer solution as mentioned before and the degradation of hydrogel was monitored gravimetrically at various intervals of time. The experiments were performed at 37° C. in PBS. The lactate based photopolymerized hydrogel completely degraded in 22 days (at 37° C., in PBS).

[0095] Thus, the macromers can be photopolymerized to form thermoresponsive hydrogels which degrade under physiological conditions.

[0096] The macromers and related prior art materials are referred to herein in the form XXXLLAA, where XXX is either part of the trade name of a precursor polymer (e.g., L81 for Pluronic™ L81 poloxamer) or refers to another property of the base polymer (e.g., 8K for 8,000 nominal Dalton PEO). LL denotes the terminal block, typically of a degradable hydroxy acid (e.g., L5 denotes an average of 5 lactate residues per arm of the polymer), where L, G, C and TMC or T represent, respectively, lactate, glycolate, epsilon-caproate, and trimethylenecarbonate. AA represents a terminal group; for example, A is for acrylate, so A2 would represent 2 acrylate terminations on the macromer as a whole.

EXAMPLE 2

Dextran Release by F127A2

[0097] The non-degradable material, F127A2, was made as described above in Example 1, with no addition of hydroxy acid to the Pluronic™ polymer backbone. Dextran (labeled with fluorescein) of molecular weight 71,000 daltons was mixed at 1% final concentration with F127A2 macromer (final concentration 10% wt/vol, in water) and polymerized as described in Example 1. Release of dextran was determined by visible absorbance. Release kinetics were significantly altered by temperature, as shown in **FIG. 3**.

EXAMPLE 3

Synthesis of Macromers with Biodegradable Linking Groups

[0098] Four monomer types were made by the general procedures described in Example 1, each containing about 4 units of each of four different biodegradable linkers, designated by L (lactate), C (caprolactone), G (glycolide), and TMC (trimethylene carbonate). Parameters for the synthesis of the thermosensitive macromonomers are listed in Table 2. Properties of the monomers characterized are listed in Table 3, including biodegradable segment and end group incorporation by HPLC and NMR, and Mn determined by GPC and NMR.

TABLE 2

Compound	M.W. (g/mole)	PPO M.W.	PEO M.W	Feed Ratio Monomer/diol	Temp ° C./time (h)	Yield (g)
F127L4A2	12600	3780	8820	4	180–190/5	80.46
F127C4A2	12600	3780	8820	4	180–190/5	81.38
F127G4A2	12600	3780	8820	4	180–190/5	71.89
F127TMC4A2	12600	3780	8820	4	180–190/5	79.29

[0099]

TABLE 3

Macro-monomer	Biodeg. Seg. Incorp. (HPLC)	Biodeg. Seg. Incorp. (MNR)	End Group Incorp. (HPLC)	End Group Incorp. (NMR)	Mn GPC g/mol	Mn NMR g/mol	Mn Expected g/mol
F127-L4A2	5.68 ± 0.01	5.58	2.09 ± 0.01	2.00	10800	11316	12998
F127-G4A2	5.39 ± 0.02	5.04	2.05 ± 0.02	2.31	10800	10804	12942
F127-C4A2	5.49 ± 0.02	5.45	2.09 ± 0.03	2.11	10000	13062	13166
F127-TMC-4A2	—	3.26	2.08 ± 0.03	2.09	12100	NA	—

[0100] The monomers differed in their rate of polymerization and rate of degradation. The long UV photopolymerization profiles are shown in **FIG. 4**. The in vitro degradation profiles of the crosslinked hydrogels are shown in **FIG. 5**.

[0101] The macromers had similar biocompatibility profiles, as shown in **FIG. 6**, as measured by the HFF cell adhesion test. In **FIG. 7**, release rates of fluorescent dextran at 37° C. and 0° C. is shown for a prior art material (F127A2) and for macromers with degradable hydrophobic blocks formed of lactide (F127L4A2), glycolide (F127G4A2) and caprolactone (F127C4A2). A longer period of quasi-zero order delivery, after the initial burst, and a distinct difference in the rates of efflux between the lower and higher temperatures, is obtained with the macromers including the degradable blocks, in comparison to the prior art material. In **FIG.**

8, the transition temperatures (for volume change and change of dextran release rate) are shown as a function of macromer concenration in the gel for the above materials and also a trimethylene carbonate based material (F127TMC4A2), a "reverse" meroxapol material with lactide (25R8LAA2), and a "normal" material (F68 L4A2) of equivalent hydrophobicity.

[0102] The HFF test was conducted as follows:

[0103] a.) Preparation of Gel

[0104] 0.5 gram of test material was dissolved in 4.5 ml standard reconstitution solution (Irgacure 1200 ppm, 3% Pluronic F127). The solution was filter sterilized using 0.2 micron filter. In a sterile hood, a glass coverslip (18 mm sq) was sterilized using 70% ethanol and was placed in a 6 well, 35 mm tissue culture dish. 200 μL of the sterile macromonomer solution was spread on a sterile coverslip. The solution was then exposed to long wavelength UV light (Black Ray, 20 mW/cm2, 1 minute) to form a gel.

[0105] c) Preparation of Cell Suspension

[0106] Human foreskin fibroblasts (HFF) cells were purchased from ATCC. Cells were used at a passage 22-23. HFF cells were cultured in a standard tissue culture ware in a humidified atmosphere containing 5% CO_2. Cells were detached from the culture flask using a 3 ml trypsin/EDTA solution (0.05% /0.53 mm) and centrifuged (2500 rpm, 3 minutes). The cell pilot was resuspended in cell culture medium (DMEM +10% FCS) at a concentration of 250000 cells/ml.

[0107] d) Cell Attachment Assay

[0108] The gels were washed with 3 ml DMEM (Dulbecco's Modified Eagles' Medium) solution and then seeded with 25000 cells/cm2 cell density. After 18 h, the gel surface and tissue culture polystyrene surface were observed under microscope and photographed. The gels were separated from coverslip and transferred into a new petri dish. The cells adhered to the gels were detached using 3 ml trypsin/EDTA (0.05%/0.53 mm) solution. A Coulter counter was used to determine the cell density.

Example 4

Effects of Linking Group Hydrophobicity on Small Molecule Delivery

[0109] Micelle-forming biodegradable macromers were synthesized and characterized which included a a non-thermosensitive core. The macromers illustrated the effects of hydrophobicity on delivery capacity for small hydrophobic molecules. The macromers were formed by synthesizing copolymers of PEG (molecular weight 8000) with different combinations of polycaprolactone and polyglycolate which were then end capped with acrylate moieties. The structures are shown in **FIG. 9**, where p is the number of glycolic acid groups and q is the number of caprolactone groups. Hydrophobicity of the mixed hydroxy acid blocks increases from A to D. The ability of these monomers to solubilize model hydrophobic drugs was demonstrated by a study of the CMC through the gradual dissolution of a molecular probe, 1,6 diphenyl 1,3,5-hexatriene (DPH). effect of hydrophobicity on drug incorporation into gels

[0110] a) Synthesis of Monomers

[0111] The molecular structures of the monomers are shown in **FIG. 9**. Polyethylene glycol 8000 (Union Carbide) was melt-dried at 100-110° C. in vacuum (10-15 mm Hg) for 4-6 hours. Caprolactone (predistilled, Aldrich), and glycolide, were charged at appropriate ratios into a Schlenk-type reaction vessel and stannous 2-ethyl hexanoate (Sigma) was added as a ring opening catalyst. The reaction was carried out for 4 hours in an inert atmosphere at 180° C. The reaction mixture was then cooled to 80° C., dissolved in toluene, precipitated in hexane and the product was collected by vacuum filtration. The product was redissolved in toluene and dried by azeotropic distillation.

[0112] Acrylation was carried out by the dropwise addition of a 2 molar excess of acryloyl chloride and triethylamine under a nitrogen flush at 65° C. for 1 hour. By-product salts were removed by vacuum filtration.

[0113] The product was isolated by precipitation in a large excess of hexane followed by vacuum filtration. The monomers were characterized by NMR on a Varian 300 MHz nuclear magnetic spectrometer.

[0114] b) Determination of Critical Micellar Concentrations

[0115] The hydrophobic dye 1,6, diphenyl 1,3,5-hexatriene (Aldrich), (DPH), which demonstrates enhanced absorbance (356 nm) at the CMC due to associative interactions, was used in this study. Alexandridis et al., *Macromolecules,* 27:2414 (1994). A stock solution of DPH was prepared in methanol (0.4 mM). Aqueous monomer solutions were prepared by dissolution in PBS and dilution to the desired concentrations. 10 μl of the dye solution were added to each vial with equilibration for at least 1 hour. The absorption spectra of the polymer/dye/water solutions were recorded in the 250-500 nm range using a Hitachi UV-VIS Spectrometer.

[0116] c) Photopolymerization

[0117] Photopolymerization of the polymer solutions were carried out in both visible and ultraviolet light systems as described in: Sawhney A. S. et al., *Macromolecules,* 26: 581 (1993); and PCT WO 93/17669 by Hubbell J. A. et al.

[0118] d) In Vitro Degradation

[0119] 200 μl of 10% monomer solution were UV polymerized to form a gel. The degradation of the hydrogels was monitored at 37° C. in PBS.

[0120] e) Results

[0121] In the synthesis, hydrophobic segments of the monomers were changed by using various combinations of caproate and glycolate linkages in the molecule. The critical micellization point was obtained from the first inflection of the absorption vs. concentration curve. The curves are shown in **FIG. 10** It is evident from the curves that the solubility of the dye is enhanced with increasing concentration of the monomer. The CMC values during aggregation

and photopolymerization for various monomers are listed in Table 4.

TABLE 4

Monomer	Critical Micellar Concentration (%)	Gel* Time Initiated Using UV Light (secs)	Gel** Time Initiated Using Visible Light (secs)	Total Degradation time (days)
A	0.92	5.5 ± 0.4	8.9 ± 0.1	10
B	0.55	5.8 ± 0.1	8.2 ± 0.5	14
C	0.32	5.2 ± 0.2	9.8 ± 0.4	16
D	0.28	4.6 ± 0.1	10.4 ± 0.3	44

*2,2-Dimethoxy-2-phenylacetophenone as UV initiator, Long UV light, 20% monomer conc.
**Eosin, triethanolamine initiating system; green light source, 20% monomer conc.

[0122] The CMC value is lowered with increase in caproate content of the monomer. This may be due to the tighter aggregation of the hydrophobic caproate moieties. The fast gelling ability of these monomers under UV and visible light is illustrated in Table 4. The gel times range between 4-12 seconds. The photopolymerized hydrogels degrade under aqueous conditions. The degradation times, i.e., times to substantially complete dissolution, varied from 10-44 days, increasing with cap/gly ratio. The fast gelation times of these monomers, their ability to dissolve hydrophobic solutes and their controlled degradation rates render them excellent candidates for localized drug delivery.

EXAMPLE 5

Synthesis of Macromers Forming Liquid Crystal Phases

[0123] a) Synthesis of Macromers.

[0124] P105L4A2, P84L5A2 and T904L5A2 macromers were synthesized by standard procedures, generally as described in Example 1, from commercial base polymers (P105 Pluronic™ poloxamer; T904 Tetronic four-armed ionic-group containing polaxamer; P84 Pluronic reverse poloxamer, or meroxapol).

[0125] b) Characterization of Optical Effects and Drug Release Properties

[0126] Aqueous solutions were prepared, and observed for anomalous optical effects ("Schlieren") without crosslinking. Rates of release of a drug were observed, wherein the drug had a molecular weight about 500 D, and substantial water solubility, as well as a hydrophobic region.

[0127] Aqueous solutions of all three macromers formed "Schlieren" type liquid crystalline phases at concentrations of 55% and higher, at room temperatures. A temperature study of the LC phases showed that the LC phases for P84L4A2 and T904L4A2 are not stable at temperatures higher than 30-35° C. The LC phase for these two polymers "phase separates" into two phases at T>35° C., one being an isotropic polymeric phase that is not transparent to light and another phase that seemed to consist of water. In contrast, a concentrated solution of P105L4A2 (75% w/v) displays a highly anisotropic LC phase that maintains its stability to temperatures up to 110° C.

[0128] Aqueous solutions of P105L4A2 (in high concentrations) formed a highly anisotropic liquid crystalline phase (LC phase) that results in good drug entrapment to slow down release. It was also observed that P84L5A2 and T904L5A2 had significant differences in the self-assembling characteristics (LC). It is possible that the drug is entrapped in the stable, highly oriented LC Phase of a p105L4A2/water system. P84L4A2 and T904L4A2 form LC phases with water, but these phases are not stable above 30-35° C. At higher temperatures, the drug as well as some of the water are excluded from the polymeric domains.

EXAMPLE 6

Treatment of Burns

[0129] The pluronic poloxamer based macromonomers, such as F127-TMC acrylate, have a "paste-like" consistency at temperatures above 37° C., and have flow characteristics at low temperatures. A "cool" formulated solution, optionally containing an appropriate drug (such as an antibiotic) is poured on a burn site, providing instant relief. At body temperatures, the formulation gels to a paste like consistency. The gel is then crosslinked, preferably by the action of light on an included photoinitiator. The characterization of photopolymerized hydrogels as carriers for therapeutic materials to influence wound healing is described in Sawhney et al., "The 21st Annual Meeting of the Society for Biomaterials," Mar. 18-22, 1995, San Francisco, Calif., Abstract, the disclosure of which is incorporated herein by reference.

[0130] The hydrogel layer on the skin provides transdermal delivery of drug to the burn site; maintains high moisture levels on severely burned sites, thus preventing dehydration; adheres strongly to the damaged tissue, and is elastic, thus preventing delamination and "peeling" of the hydrogel dressing; and absorbs exudate from the wound. After a suitable time, controlled by the nature of the lining group (trimethylene carbonate in this example, giving a residence time of over a week), the gel will dissolve into components which are absorbable or innocuous. It has been demonstrated in other experiments that related gel formulations, based on a polyethyleneglycol backbone such as the material 8KL5A2 (i.e,. PEO of molecular weight 8,000, with 5 lactate groups on each end terminated with acrylate groups), do not retard the healing of full thickness biopsy wounds in rat skin. The pentablock polymer F127-TMC acrylate of Example 3 is improved in comparison to the prior-art 8KL5A2 polyethylene glycol-based triblock formula in that it gels spontaneously on the burn site, and thus does not tend to run off the site before it can be photocrosslinked.

EXAMPLE 7

Use of Hydrophobic Macromers to Increase Tissue Adherence

[0131] Use of macromers carrying one or more hydrophobic groups can improve the adherence of a hydrogel to a biological material. A macromer having having this property was synthesised. The base polymer was a Tetronic™ 4-armed polymer based on ethylene diamine, where each arm is a PEG-PPO-PEG triblock copolymer. The base polymer was extended with lactide as previously described in Example 1, and then capped with about two moles of palmitoyl chloride per mole of polymer, in order to cap

about half of the arms. The remainder of the hydroxyls were capped with acroyl chloride, as described in Example 1. The resulting macromer was dispersed in water and was polymerized in contact with tissue, to which it adhered tenaciously.

EXAMPLE 8

Formation of Microspheres

[0132] Pluronic™ based biodegradable macromers made as described above above, such as the materials of Example 3, in an aqueous solution formed micelles with a CMC value ranging from about 1% to 5 % w/v. After photopolymerization, the structure of the micelle is substantially preserved.

EXAMPLE 9

Synthesis of F127-Dimer Isocyanate-F127 Lactate Acrylate

[0133] Two molecules of a macromer diol (Pluronic F127) are coupled with one molecule of a diisocyanate (dimer isocyanate) to produce higher di- and tri-functional alcohols, to provide macromers with high elasticity, high distensibility and high tissue adherence.

[0134] The following reagents are used: Pluronic F127 (BASF lot # WPM N 581B, Mn=12200); dimer isocyanate (DDI-1410, Henkel Lot # HL 20037, % NCO =14.1%); and dibutyltin dilaurate.

[0135] Synthesis of F127-DDI-F127: 366 g of Pluronic F127 was heated to 100° C. under vacuum for four hours to produce a melt. DDI-1410 (8.94 g) and dibutyltin dilaurate (0. 115 g) was added to the melt (melt temperature 70° C.) and stirred vigorously for 4 hours. The mixture readily crystallized when cooled. Product was a white waxy crystalline material. Theoretical molecular weight=24,996 Daltons.

[0136] Synthesis of F127-DDI-F127 Lactate, diol: 100 g of F127-DDI-F127 was dried for 4 hours under vacuum at 100° C. 4.67 g of (D,L) Lactide was charged to the reaction pot under an argon flush. Stannous 2-thyl hexanoate (0.5 mole percent) was added to the reaction. The melt was vigorously stirred at 150° C. under argon for 4 hours. The product was isolated by precipitation in hexane, followed by filtration. The product was a white, crystalline, flaky material.

[0137] Synthesis of F127-DDI-F127 Lactate, acrylate: 100 g of F127-DDI-F127 Lactates diol was charged into a 1000 ml three-necked reaction vessel. 800 ml of toluene (Aldrich, 0.005% water content) was added to the flask. 50-75 ml of toluene was azeotroped off to ensure moisture free reactants 2.427 ml of predistilled triethylamine, followed by 2.165 mls of acryloyl chloride was added to the reaction mixture at 65° C. After one hour of reaction time, the turbid reaction mixture was filtered, and isolated into a white powder by precipitation into a large excess of hexane. The product was collected by vacuum filtration and dried to a constant weight.

[0138] Molecular structure determination was carried out by NMR, IR. The product was found to be soluble in water and crosslinkable by visible and UV light. Percent water uptake of fully cured 10% w/w hydrogels=22. 1%. Hydrogels formed by photopolymerization at 10% concentration while on dead bovine tissue were determined to be generally well adherent.

[0139] P105-DDI-P105 lactate acrylate and L81-DDI-L81 lactate acrylate was synthesized from the respective Pluronic poloxamer starting materials (P105,L81) by the procedure described above. These macromers were insoluble in water. They were used to encapsulate bioactive molecules in hydrophobic matrices to achieve sustained drug release.

EXAMPLE 10

Synthesis of F127-DDI-F127 Isophorone Isocyanate

[0140] The synthesis and polymerization of a macromer which crosslinks without involving free radical polymerization is demonstrated. 50 g of F127-DDI-F127 diol, prepared as in Example 9, was dissolved in 100 ml of toluene in a three necked reaction flask. 90 ml of toluene was distilled off azeotropically at 110° C. under argon. The flask was maintained at 100° C. for 12 hours under vacuum (12 mm Hg). The reaction flask was then cooled to room temp, and 200 ml of dry methylene chloride was added to the reaction flask. 0.445 g of isophorone isocyanate (Aldrich) was added (in a bolus) to the reaction flask at approximately 30° C. 0. 15 g of dibutyltin laurate was added to the reaction mixture. The reaction mixture was stirred under argon at 30° C. for 12 hours, and precipitated in 1000 ml of hexane (EM Sciences). White flakes were collected by vacuum filtration, and rinsed with 150 ml of hexane. The product was dried in a vacuum oven to a constant weight. Characterization by NMR, IR showed synthesis of the expected material.

[0141] The polymerizability of F127-DDI-F127 isophorone isocyanate was evaluated. Partially dried product (0.16 g) was added to 1.44 g of deionized water. The product initially formed bubbles in contact with water, then dissolved over approximately 3 days to form a viscous solution. To test polymerizability, 200 mg of F127-DDI-F127 isophorone isocyanate solution of polyethyleneimine in methylene chloride. The solution was stirred vigorously for a few seconds. A gelatineous product was observed. Gel time: 5.9 seconds. Polyethyleneimine is believed to have hemostatic properties; this formulation thus is potentially suitable for a topical wound dressing. In addition, structures formed of these materials can be used as drug depots.

EXAMPLE 11

Effect of Hydrophobicity on Drug Release Kinetics for Bulk Devices

[0142] Macromers were synthesized having a wide range of hydrophobicities ranging from 0-90% PPO content. All macromers were tested at 15% macromer concentration except those whose PPO content was greater than 60% which were used neat. **FIG. 13** shows the rate of release of a small drug from gels of these macromers. At 10 and 15% macromer loading (8KL10, prior art; 25R8L4A2, based on a "reverse" Pluronic polymer) and PPO content of less than 60% hydrophobic partitioning did not show a significant effect on prolonging 500 Da sparingly soluble drug release Devices prepared with neat macromers (PPO content >60%; P84L5A2 and L81L5A2, synthesized by general procedures as described above) showed a significant ability of these highly hydrophobic, dense macromers to retard water per-

meation and drug dissolution. In the extreme case (L8lL5A2; PPO content=90%), the release kinetics showed first order release with half of the drug being released from the device over 17 days with the remainder being eluted from the device over a total of 66 days.

Example 12

Effect of Polymer Hydrophobicity on Drug Diffusivity

[0143] Membranes of constant thickness were prepared from neat macromers of Example 11, and used as the diffusion barrier in a two-compartment dialysis cell. **FIGS. 14 and 15** show the increase in the concentration of 500 Da drug in the receptor side of the cell over time. The diffusion coefficient calculation was based on the following relationship:

$$D=J/(A*(\Delta C/\Delta\chi)$$

[0144] where D is the diffusion coefficient, J is the measured flux, A is the exposed area of the film, ΔC is the concentration gradient across the film and $\Delta\chi$ is the average film thickness. The diffusion coefficients for macromers having 50% (P105L5A2) or 90% (L81L5A2) relative hydrophobic domain and were calculated to 1.6×10^{-9} cm^2/sec and $5.63\times10^{-10}cm^2$/sec, respectively. Thus, diffusion was faster in the more hydrophobic material, as expected for a drug of low water solubility.

EXAMPLE 13

Release of Tetracycline and Taxol

[0145] A 30% w/w solution of F127 trimethylene carbonate acrylate (as described in Example 3) in phosphate buffered saline, pH7.4 was prepared. 3000 ppm Darocur™ (Ciba Geigy) was incorporated in the solutions as photoinitiator. Tetracycline (free base, crystalline, F. W. 444.44) was incorporated in the macromer solution by equilibration for 12 hours at 37 degrees C. Then, 200 microliters of the solution was crosslinked by UV light (10 W/cm2, full cure). In vitro release of tetracycline from the 200 microliter cured gel, after a brief rinse, was carried out in 5 mls PBS, pH 7.4, 37° C. The PBS was exchanged daily to ensure "sink" conditions. The release profile is seen **FIG. 16**. After an initial burst, tetracycline was released steadily for nearly a week.

[0146] Taxol was incorporated into gels by similar procedures, except that Tween surfactant was used to solubilize the Taxol concentrate. A similar release pattern to that seen with tetracycline was observed.

EXAMPLE 14

Urethane-containing Macromers

[0147] PEO of molecular weight 1450 was reacted with approximately 1 mole of lactide per end, using procedures described above, to give 1.4KL2. The 1.4KL2 was weighed into a 100 ml flask (8.65 g) and 270 ml of dried toluene was added. About 50 ml of toluene was distilled off to remove residual water as the azeotrope, and the solution was cooled. Then 0.858 g (825 microliter) of commercial 1,6 hexanediisocyanate was added, and also 1 drop of dibutyltindilaurate (ca. 0.02 g). The solution was at 60 degrees at addition, and warmed to 70 degrees over about 10 minutes. Heat was applied to maintain the solution at about 75 degrees for about 3.5 hours. NMR and IR spectra confirmed consumption of the diisocyanate, and the resulting solution was therefore expected to contain alternating PEO and hexane blocks, linked by urethane linkages, and terminated by hydroxyls. This material can be capped with reactive end groups, optionally after further extension with hydroxy acids, to form a reactive macromer. The urethane links and hexane blocks are present to promote tissue adherence.

[0148] Modifications and variations of the present invention will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the following claims.

What is claimed is:

1. A macromer which is capable of forming a gel, the macromer comprising at least four covalently linked polymeric blocks, wherein

a) at least one block is hydrophilic

b) each hydrophilic block individually has a water solubility of at least 1 gram/liter; and

c) at least two blocks are sufficiently hydrophobic to aggregate to form micelles in an aqueous continuous phase;

wherein the macromer further comprises at least one crosslinkable group.

2. The macromer of claim 1 wherein the crosslinkable groups are separated by at least one degradable linkage capable of degrading under physiological conditions.

3. The macromer of claims **1** wherein at least one hydrophobic block is separated from any crosslinkable group by at least one hydrophilic block.

4. The macromer of any of claim 1 comprising five total blocks.

5. The macromer of claim 1 comprising at least two chemically distinct hydrophobic blocks.

6. A solution of a macromer of claim 1, further comprising a biologically active material.

7. The macromer of claim 1 wherein the macromer comprises at least one thermally sensitive region, and wherein a solution of the macromer is capable of gelling or crosslinking to produce a hydrogel with a temperature dependent volume.

8. The macromer of claim 7 wherein the rate of release of a drug incorporated in the hydrogel is dependent upon the volume of the hydrogel.

9. The macromer of claim 1 wherein the macromer is capable of thermoreversible gelation in an aqueous solution of the macromer at a concentration of at least 2% by weight, and wherein the gelation temperature is between about 0° C. and about 65° C.

10. The macromer of claim 1 wherein the macromer has an optically anisotropic phase at a concentration at or below the maximal solubility of the macromer in an aqueous solution, at a temperature between about 0 and 65° C.

11. The macromer of claim 1, further comprising at least one ionically charged moiety covalently attached to the macromer.

12. The macromer of claim 1 wherein the macromer has a phase transition temperature in the range of 0 to 100° C., and wherein the transition temperature is affected by a property selected from the group consisting of the ionic

composition of an aqueous solution of the macromer and the concentration of macromer in the aqueous solution.

13. A mixture comprising the macromer of claim 1 and a hydrophobic material non-covalently associated with the macromer.

14. The mixture of claim 13, wherein the hydrophobic material is selected from the group consisting of a hydrocarbon, a lipid, a fatty acid, and a sterol.

15. The macromer of claim 1 wherein the crosslinkable group is selected from the group consisting of an ethylenically unsaturated group, an epoxide, an isocyanate, an isothiocyanate, an aldehyde, an amine, a sulfonic acid and a carboxylic acid.

16. The macromer of claim 1 wherein the hydrophobic blocks are the same or different and are selected from the group consisting of polypropylene oxide, polybutylene oxide, hydrophobic mixed poly(alkylene oxides), and oligomers of hydroxy acids, lactones, amino acids, anhydrides, orthoesters, phosphazenes, and phosphates.

17. The macromer of claim 1 wherein the hydrophilic blocks are the same or different and are selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly-(ethyloxazoline), polysaccharides and amino acid polymers.

18. The macromer of claim 2 wherein the degradable linkage groups are the same or different and are selected from the group consisting of poly(alpha-hydroxy acids), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(phosphazines), poly(phosphoesters), and polylactones.

19. The macromer of claim 1 wherein at least two hydrophobic blocks are separated by a hydrophilic block.

20. The macromer of claim 1 wherein each hydrophobic block is separated by a hydrophilic block from any other hydrophobic block.

21. The macromer of claim 1 wherein the dry macromer absorbs at least about 10% in weight of water.

22. The macromer of claim 1 wherein the molecular weight of the macromer is at least 1000 Daltons.

23. The macromer of claim 1 wherein the molecular weight of the macromer is at least 2000 Daltons.

24. The macromer of claim 1 wherein the molecular weight of the macromer is at least 4000 Daltons.

25. A gel formed from an aqueous solution of the macromer of claim 1 or mixtures thereof, wherein the crosslinkable groups are covalently crosslinked.

26. The gel of claim 25 further comprising a biologically active material.

27. The gel of claim 26 wherein the biologically active material is provided in a form selected from the group consisting of particles, microparticles, pro-drug conjugates, or liposomes.

28. The gel of claim 25 wherein the gel changes in permeability in response to one or more effects selected from the group consisting of changes in temperature, pH, ionic strength, and ionic composition.

29. The gel of claim 25 wherein the gel is formed on a surface of biological tissue.

30. The gel of claim 25 wherein the gel is formed on a surface of a medical device.

31. The gel of claim 25 wherein the gel is formed between opposed surfaces, tending thereby to adhere said surfaces.

32. A method of treating a medical condition, comprising applying to tissue in vivo an aqueous solution of a gel-forming macromer, comprising at least four covalently-linked polymeric blocks, wherein

a) at least one blocks is hydrophilic;

b) each hydrophilic block individually has a water solubility of at least 1 gram/liter; and

c) at least two blocks are sufficiently hydrophobic to aggregate to form micelles in an aqueous continuous phase; and

wherein the macromer further comprises at least one crosslinkable group.

33. The method of claim 32 wherein the aqueous solution comprises a solution or suspension of a biologically active material.

34. The method of claim 33 wherein the medical condition is a burn or abrasion of the skin.

35. The method of claim 33 wherein the medical condition is a tissue disturbed by a surgical intervention.

36. The method of claim 35 wherein the surgery is angioplasty.

37. The method of claim 35 wherein the surgery is conducted through the cannula of a trocar.

38. A method for controlling the rate of delivery of a biologically active material, comprising mixing the active material with a solution of a gel-forming macromer and covalently crosslinking said macromer to form a gel, wherein the macromer comprises at least four blocks and at least one covalently crosslinkable group, and wherein at least two the blocks are hydrophobic, and at least two of the blocks are hydrophilic.

39. The method of claim 38 wherein the crosslinked gel changes in permeability in response to an effect selected from the group consisting of a change in temperature, a change in ionic concentration, and a change in pH.

40. The method of claim 38 wherein at least one hydrophobic block aggregates in aqueous solution to form a hydrophobic domain.

41. The method of claim 40 wherein the hydrophobicity of said domain is controlled by selecting the hydrophobicity of the block.

42. The method of claim 40 wherein the hydrophobicity of said domain is controlled by adding hydrophobic materials to the gel-forming macromer solution.

43. The method of claim 38 wherein the active material is in the form of a microparticle.

44. The method of claim 38 wherein the gel forms a microparticle after crosslinking.

45. The macromer of claim 1 further comprising at least two hydrophilic blocks.

46. The macromer of claim 1 provided in a pharmaceutically acceptable carrier.

47. The macromer of claim 46 wherein the macromer is provided in a carrier suitable for parenteral administration.

48. The method of claim 32 wherein the macromer further comprises at least two hydrophilic blocks.

49. The method of claim 32 wherein the macromer is applied to tissue in a pharmaceutically acceptable carrier.

50. The method of claim 49 wherein the macromer is provided in a pharmaceutically acceptable carrier for parenteral administration.

* * * * *

Electronic Patent Application Fee Transmittal

Application Number:	11083167
Filing Date:	17-Mar-2005
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Filer:	Darlene Vanstone/Hollie Wakefield
Attorney Docket Number:	4000.3010 US1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	7556441
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Hollie Wakefield
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	05-MAY-2010
Filing Date:	17-MAR-2005
Time Stamp:	15:17:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	1490
Deposit Account	502807
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment Copy Claims/Response to Suggested Claims	Amendment.pdf	106722 9ba19b2a556fb4ed45b53f0a02ded7e3e46e862b	no	12
Warnings:					
Information:					
2	Extension of Time	ExtTime.pdf	43450 d3fe8ba10186de331eb219571f493b9354487147	no	1
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	ExhibitA.pdf	215806 1336d06b48ab33cc9b41a02c1092639b028db0ef	no	16
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	ExhibitB.pdf	871237 46ddd2a764824704116daa23084c2c3f0d308118	no	11
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	ExhibitC.pdf	172633 444659f124096c50b817130f8d95a6f0c3721233	no	17
Warnings:					
Information:					
6	Miscellaneous Incoming Letter	ExhibitD.pdf	149778 5eb6e7b65d89048c7dc4e942bb19c13e97c53d14	no	13
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	ExhibitE.pdf	311935 6ce56ef5ae99f96d64984dfaa34f14f2087bf5ef	no	23
Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	29979 63cb77ad3f8c6af21525b0015eb3895f5594c268	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1901540		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/083,167	03/17/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/05/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 47	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 2	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/JOSEPHINE DOUGLAS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1	8002

38421 7590 01/06/2010

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
01/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/083,167	EHRICH, ELLIOT	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 26* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/22/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of October 5, 2009 made to the office action filed May 5, 2009. Claims 1-23 and 26 are pending. Claims 24 and 25 are cancelled and claims 3-5 are withdrawn. Claims 1, 2, 6, 15, 18, 20 and 22 are amended and claim 26 is new.

The declaration filed October 5, 2009 has been considered and found persuasive. Particularly, the Applicant's application exhibits a serum AUC of naltrexone at least about three times or at least about two times greater than that achieved by 50 mg/day oral administration, whereas the formulation of Tice is similar to a 50 mg/day oral administration. In light of the declaration and/or the Applicant's arguments, the 35 U.S.C. 102(b) and 103(a) rejections are withdrawn.

In light of the amendments to the claims, the 35 U.S.C. 112 second paragraph rejection of claims 6, 18, 20 and 22 is withdrawn.

The Examiner identified allowable subject matter, wherein claim 1 is amended to include the polymer of claim 22, but the Applicant's did not agree to the amendments.

Due to the withdrawal of all previous rejections and further consideration, the new 35 U.S.C. 112, first paragraph rejection is below, thus providing a NEW Non-Final rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when

assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration."

(2) The breadth of the claims:

Claims 1, 2, 6-23 and 26 embrace and reads on any long acting naltrexone formulation. The specification does not enable any long acting naltrexone formulation that gives a serum AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration.

(3) The state of the prior art:

The state of the art regarding any long acting naltrexone formulation providing a serum AUC of naltrexone at least about two or three times greater than that achieved by

50 mg/day oral administration is very low. Tice et al. teach muscular injectable naltrexone microsphere compositions and their use in reducing consumption of heroin and alcohol (see title and abstract). The composition comprises a matrix consisting of the polymer poly-(D,L-lactide) The naltrexone is released in a controlled manner for greater than 28 or about 32 days. Smaller doses may be administered after the first dose, because on continues to obtain release from the prior injected mirospheres to which is added the release from the lately administered microspheres, or one can enjoy enhanced levels of the naltrexone without increasing the amount of the microspheres which are administered (see abstract and column 6, lines 19-29). The microspheres are formulated from about 150-350 mg of naltrexone such that the plasma concentration is in a therapeutic range of at least about 2 ng/mL (see column 4, lines 36-38 and column 5, lines 60-63; addresses claims 1, 2, 6 and 9-13). The microsphere formulation gave an AUC of 1.19 times greater than that achieved by 50 mg/day oral administration (see column 14, lines 40-55). Naltrexone is employed in an amount in the range of 15 to 50 weight % (see claim 1).

(4) The predictability or unpredictability of the art:

The predictability of every long acting naltrexone formulation providing an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration is relatively low. In other words, just because there are potential of a long acting formulation of naltrexone to provide an AUC of naltrexone at least about two

or three times greater than that achieved by 50 mg/day oral administration, effective elevated AUC serum levels has yet to be completely established. As Tice et al. teaches, every long acting formulation of naltrexone does not give an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration. Therefore, because there is a "potential" or reaching the claimed AUC serum values, the actual long acting formulation that gives these results is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Tice et al.

(6) The amount of direction or guidance presented / working examples:

The specification as filed does not speak on or show any working examples any studies performed that any long acting formulation provides an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. In the instant case, the guidance of the specification as to any long acting formulation providing an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration tration is completely lacking.

Particularly, the specification teaches that the long acting formulation comprising DL PLGA (poly(lactide)-co-glycolide polymeric matrix (i.e. MEDISORB; see page 12, line 2; and page 15, line 1) in conjunction with psychosocial treatment is effective in treating heavy drinking (see page 24 in its entirety). In regards to its comparison to oral naltrexone, a definitive comparison of efficacy can not be made (see page 26, lines 5-10), but the Applicants attempted to compare the invention to other oral administration studies to show that the invention was effective in treating acohol dependence with psychosocial therapy, than psychosocial therapy alone (see page 28 in its entirety and page 29, lines 1-5).

(7) The quantity of experimentation necessary:

The instant claims read on any long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. As discussed above the specification fails to provide any support for any long acting formulation wherein the serum AUC of naltrexone is at least about three times greater than that achieved by 50 mg/day oral administration. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every one of polymer and combination of ingredients to comprise a formulation of naltrexone, or at least a subset with specific ingredients that is sufficiently representative of specific long

acting naltrexone formulations, to determine if each formulation has a serum AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration. For example, to test for the claimed AUC, different formulation comprising different polymers and other ingredients including naltrexone, would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration since parenteral administration can include several routs) would also have to be selected. Serum AUC measurements would have to be taken and then compared to the oral administration route. If desired serum AUC results did not result, the dosage regime and/or formulation would have to be varied, for example by changing the dosage amount or route of administration, until the desired serum AUC results were achieved. If the desired serum AUC measurements were shown with a particular formulation, then another formulation would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each formulation to determine if the formulation has a serum AUC of naltrexone that is at least about two or three times greater than that achieved by 50 mg/day oral administration, in order to be able to fully carry out the invention. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is not enabled for a long acting formulation provides an AUC of naltrexone at least about two or three times greater than that achieved by 50 mg/day oral administration

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kendra D Carter/

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

PTO/SB/08a (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11083167
Filing Date	2005-03-17
First Named Inventor	Elliot Ehrich
Art Unit	1617
Examiner Name	Kendra D. Carter
Attorney Docket Number	4000.3010 US1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.C./	1	20040151774	A1	2004-08-05	Pauletti et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11083167
	Filing Date	2005-03-17
	First Named Inventor	Elliot Ehrich
	Art Unit	1617
	Examiner Name	Kendra D. Carter
	Attorney Docket Number	4000.3010 US1

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Kendra Carter/	Date Considered	01/01/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11083167	EHRICH, ELLIOT
	Examiner	Art Unit
	KENDRA D CARTER	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/12/2009	04/29/2009	12/31/2009						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	N	N						
	4	÷	N	N						
	5	÷	N	N						
	6	÷	✓	✓						
	7	÷	✓	✓						
	8	÷	✓	✓						
	9	÷	✓	✓						
	10	÷	✓	✓						
	11	÷	✓	✓						
	12	÷	✓	✓						
	13	÷	✓	✓						
	14	÷	✓	✓						
	15	÷	✓	✓						
	16	÷	✓	✓						
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	18	÷	✓	✓						
	19	÷	✓	✓						
	20	÷	✓	✓						
	21	÷	✓	✓						
	22	÷	✓	✓						
	23	÷	✓	✓						
	24	-	-	-						
	25	-	-	-						
	26			✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11083167	EHRICH, ELLIOT
	Examiner	Art Unit
	KENDRA D CARTER	1617

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (eDAN)	4/29/09	KDC
EAST (search included)	4/29/09	KDC
Google (search terms similar to EAST search)	4/29/09	KDC
Search updated	12/9/09	KDC

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Elliot Ehrich		
Application No.	11/083,167	Group No.	1617
Filed:	March 17, 2005	Examiner:	Kendra D. Carter
Confirmation No.	8002		

For: Naltrexone Long Acting Formulations and Methods for Use

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment is in response to the Office action mailed from the U.S. Patent and Trademark Office on May 5, 2009, in the above-identified application.

A Petition for Extension of Time for two months and the appropriate fees are being filed concurrently.

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **5** of this paper.

Amendments to the Claims:

Please add new Claim 26.

The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing:

1. (Currently Amended) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is ~~at least about two times, preferably~~ at least about three times~~, more preferably about 3.3 times~~ greater than that achieved by 50 mg/day oral administration.

2. (Currently Amended) The [[A]] method of claim 1 ~~treating an individual in need of naltrexone~~ comprising administering [[a]] the long acting formulation in a dose comprising between about 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.

3. (Withdrawn/Original) A method of treating an individual in need of naltrexone comprising administering naltrexone, in the absence of co-administering alcohol, to an individual who has not undergone alcohol abstinence within three days, such as five days, prior to the naltrexone administration.

4. (Withdrawn/Original) The method of Claim 3 wherein the naltrexone is administered in a long acting formulation comprising naltrexone.

5. (Withdrawn/Original) A method of increasing the days prior to occurrence of alcohol consumption in an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration.

6. (Currently Amended) The [[A]] method of claim 1 ~~treating an individual in need of naltrexone~~ comprising administering [[a]] the long acting formulation comprising naltrexone in a dosage between about 160 mg to about 480 mg

naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five or more days~~, such as within ten days,~~ before said administration.

7. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.

8. (Original) The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.

9. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose of at least about 160 mg of naltrexone.

10. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 160 and 240 mg of naltrexone.

11. (Original) The method of Claim 10 wherein the long acting formulation is administered in a dose of about 190 mg of naltrexone.

12. (Original) The method of claim 1 wherein the long acting formulation is administered in a dose between about 310 and 480 mg of naltrexone.

13. (Original) The method of Claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone.

14. (Original) The method of claim 1 wherein the long acting formulation is administered over a period of about 24 week period or longer.

15. (Currently Amended) The method of claim 1 further comprising a second administration of a long acting formulation comprising naltrexone at least about 7 days~~, preferably at least about 14 days, more preferably at least about 21 days, such as about 28 days,~~ after the first administration.

16. (Original) The method of Claim 15 wherein the second long acting formulation is substantially similar to the first long acting formulation.

17. (Original) The method of Claim 15 wherein the second long acting formulation is

the same as the first long acting formulation.

18. (Currently Amended) The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency~~, such as a heavy drinker~~.

19. (Original) The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.

20. (Currently Amended) The method of claim 1 wherein naltrexone is administered by injection~~, such as intramuscularly or subcutaneously~~.

21. (Original) The method of claim 1 wherein the long acting formulation comprises a polylactide polymer or a poly lactic acid polymer.

22. (Currently Amended) The method of claim 1 wherein the long acting formulation comprises a polylactide-co-glycolide polymer~~, such as a polymer which possesses a molecular weight of at least 100,000 daltons~~.

23. (Original) The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35 % by weight.

24-25. (Canceled)

26. (New) A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about two times greater than that achieved by 50 mg/day oral administration.

REMARKS

Claims 3-5 have been withdrawn. Claims 1, 2, 6, 15, 18, 20, and 22 have been amended. New claim 26 has been added. Support for claim 26 is found in claim 1 as originally filed and in the specification at page 3, line 12. Claims 1-23 and 26 are pending in the application. Reconsideration is respectfully requested.

Claim Rejections – 35 USC §112

The Examiner has rejected claims 6, 18, 20, and 22 on the grounds that the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. Applicants have amended claims 6, 18, 20, and 22 to remove the language objected to by the Examiner. Withdrawal of the rejection under this section is respectfully requested.

Claim Rejections – 35 USC §102

Claims 1, 2, 6-21 and 23 are rejected under 35 U.S.C. §102(b) as being anticipated by Tice et al. (6,306,425 B1). The Examiner states that Tice teaches muscular injectable naltrexone microsphere compositions and their use in reducing consumption of alcohol. The Examiner also states that Tice discloses a composition comprising a matrix consisting of polymer poly-(D,L-lactide). The Examiner further states that Tice discloses naltrexone being released in a controlled manner for greater than 28 or about 32 days. The Examiner states that Tice discloses that smaller doses may be administered after the first dose, because one continues to obtain release from the prior injected microspheres to which is added the release from the lately administered microspheres, or one can enjoy enhanced levels of the naltrexone without increasing the amount of the microspheres which are administered. The Examiner further states that Tice discloses microspheres that are formulated from about 150-350 mg of naltrexone such that the plasma concentration is in a therapeutic range of at least about 2 ng/ml. The Examiner *asserts* that the Tice microsphere formulation gave an AUC of more than 3.3 times greater than that achieved by 50 mg/day oral administration based on the Examiner's interpretation of Tice at column 14, lines 40-55. With regard to claims 6 and

19, the Examiner asserts that Tice teaches that the primary application for the subject formulations in an intramuscular injection that is also designed to avoid oral administration so as to increase patient compliance. With regard to claim 13 the Examiner states that Tice teaches the limitation in which the amount of naltrexone is about 380 mg because the Examiner asserts that the 350 mg dosage taught by Tice reads on about 380 mg (emphasis original). Applicants respectfully submit that the Examiner is incorrect and that the presently claimed invention is not anticipated by Tice for the reasons discussed below.

Turning first to amended claim 1 of the present invention, this claim requires that the serum AUC of a parenterally administered formulation of the invention be at least about three times greater than that achieved by 50 mg/day oral administration. Contrary to the Examiner's assertion, Tice *does not disclose* this AUC. The Examiner's interpretation of the data in column 14, lines 40-55, is *incorrect*. The column labeled "Ratio F-1/Tablets" as seen in column 14, lines 40-55, presents the mean AUC_{0-32d} ratio between Naltrexone in the injectable microsphere formulation ("F1") and Naltrexone in the oral 50 mg dose ("Tablets"). The Mean Ratio of F1/Tablets is listed in column 14, lines 40-55, of Tice as 1.18, and is obtained by dividing 1051.6 by 888.01, as found in the "Ratio" column of the table in column 14. The mean AUC_{0-32d} F1/Tablets ratio of Tice is therefore not more than 3.3 as stated by the Examiner, but is in fact more than 60% lower than 3.3. In other words, the microsphere formulation of Tice gave an AUC that is merely 1.18 times greater than that achieved by the 50 mg/day oral administration – a value that is nearly identical to the 50 mg/day oral administration. The plain reading of Tice indicates that Tice *admits* that the AUC for the daily oral dose is *similar* to that of the AUC of Formulation F-1'. For example, see column 14 lines 59-64, of Tice wherein it is states that:

> The data indicate that the exposure to the active naltrexone moiety is *likely to be comparable* whether taking *daily* 50-mg tablets for one month or one 300 mg of microencapsulated naltrexone by intramuscular injection if microsphere Formulation F-1' once monthly" [emphasis added].

Clearly, if the data in Tice showed that the injectable F-1' naltrexone formulation achieved a superior pharmacokinetic profile than the oral dose, such as three times greater, the inventors of Tice would have highlighted that result. Instead the inventors of Tice characterized the performance of the F-1' injectable formulation as *merely similar* to the daily oral dose. Indeed, none of the formulations made by Tice achieve even *twice* the AUC of the oral formulation over the same period of time. Thus, claim 1 *and* claim 26 do not embrace the formulations made in Tice. A reading of Tice as a whole establishes that the *objective* is to design formulations that are comparable to the oral dose, not at least twice or three times the oral dose. The AUC values between Tice and the presently claimed invention are not inherently the same and therefore, the claims do not embrace the formulation disclosed in Tice.

Contrast Tice to the teachings of the present application at page 3, lines 15-20, which states:

> This invention arose from the unexpected discovery that substantially improved serum levels of naltrexone can be achieved by administering long acting formulations of naltrexone, such as the Alkermes, Inc. formulation, VIVITREX® injectable suspension, made employing its MEDISORB® delivery system. Indeed, it was not expected that serum levels of about 3.3 times that achieved by a 50 mg/day oral dose could be achieved by a single IM administration of VIVITREX®.

Applicants are providing herewith a Declaration under § 1.132 by the inventor, Dr. Elliot Ehrich which discusses in more detail how this discovery came about and provides comparative data and information between Tice and the data and information upon which the present invention is based. It is clear from the Declaration and the Exhibits provided therewith that the AUC disclosed by Tice for the formulations tested therein are significantly below the presently claimed AUC for the long acting naltrexone formulations of the present invention. Therefore, claim 1 and claim 26 are not anticipated by Tice. Given that claims 2 and 6-23 have been amended to depend from claim 1 directly or indirectly claims 2 and 6-23 are also not anticipated by Tice. Withdrawal of the rejection under this section is respectfully requested.

Claim Rejections – 35 USC §103

The Examiner has rejected claim 22 under U.S.C. 103(a) as being unpatentable over Tice et al. (6,306,425 B1) as applied to claims 1, 2, 6-21, and 23 above in further view of Chandrashekar et al. (6,143,314). The Examiner applies the teachings of Tice et al. as applied to claims 1, 2, 6-21, and 23 above. The Examiner states that Tice et al. do not teach a polylactide-co-glycolide polymer. The Examiner asserts that Chandrashekar et al. teach a controlled release liquid delivery compositions of active compounds such as naltrexone with polymers such as polylactides and poly(lactide-co-glycolide) as the controlled release additive (abstract; claims 1 and 2; column 7, line 15). The Examiner concludes that one of ordinary skill in the art at the time of the invention would have found it obvious and have been motivated to combine the method of Tice et al. and a polylactide-co-glycolide polymer because it is known in the art that these types of polymers are known to provide controlled release of active ingredients. The Applicants respectfully disagree.

Claim 22 depends directly from claim 1. As discussed above, claim 1 is not anticipated by Tice as it does not disclose the presently claimed AUC of the trospium long-acting formulation of the invention as discussed in the § 1.132 Declaration filed herewith. Chandrashekar also does not disclose the presently claimed AUC of the long acting formulations of naltrexone of the invention. To establish a *prima facie* case of obvious, the prior art references when combined must teach or suggest all of the claim limitations (MPEP §2143). The cited combination of Tice and Chandrashekar do not disclose or suggest all of the presently claimed limitations.

In addition, the Declaration further elaborates on the unexpected results reported on page 3, lines 15-20, of the present application. It is well settled that unexpected results can be established by factual evidence. In re Lindner, 173 USPQ 356 (CCPA 1972). Applicants have provided this factual evidence in the specification and in the accompanying Declaration. It is also well settled that proof of unexpected properties may rebut a *prima facie* case of obviousness including differences based on longer lasting pharmacological activity where the actual increase was beyond reasonable expectations. See, *In re Chupp*, 2 USPQ2d 1437,1440 (CAFC 1987) citing In re Blondel, 499 F.2d 1311, 182 USPQ 294 (CCPA 1974) (reversing rejection of claims to

compounds which prior art suggested would have longer-lasting pharmacological activity, where actual increase was beyond reasonable expectations). Therefore, claim 22 as well as claims 1 and all claims dependent thereon and claim 26 are not *prima facie* obvious in view of the cited combination of references. Withdrawal of the rejection is respectfully requested.

A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under § 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

ELMORE PATENT LAW GROUP, P.C.

/Darlene A. Vanstone/

Registration No. 35,729
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: **October 5, 2009**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich

Application No. 11/083,167 Group No. 1617

Filed: March 17, 2005 Examiner: Kendra D. Carter

Confirmation No. 8002

For: Naltrexone Long Acting Formulations and Methods for Use

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

I, Elliot Ehrich, am the inventor of the subject matter of the above-identified application. I am also employed by Alkermes, Inc, the assignee of the above-identified application. My curriculum vitae is attached hereto as Exhibit D.

Background

The present invention is directed to the unexpected discovery that a single injection of a naltrexone-containing long-acting formulation provides systemic exposure to naltrexone (AUC) which is at least 2 fold higher over a 28 day period than the AUC of an oral regimen of 50 mg per day over a 28 day period. The invention which is described in the above identified application resulted from a discovery made during clinical trial testing of Alkermes' MEDISORB® (injectable) Naltrexone (tradename VIVITREX®). Due to the size of the lengthy full Clinical Study Report only relevant portions of the Clinical Study Report # ALK21-005 (the "Report") finalized November 9, 2004 is attached hereto as Exhibits A and B. I will be referring to this Report throughout my declaration.

Prior to obtaining the data discussed in the Report, it was believed that the doses of MEDISORB® Naltrexone suspension selected for the studies described in the Report (i.e. 190 mg and 380 mg) would result in total systemic exposure (AUC) which was similar to the AUC of an oral regimen of 50 mg per day naltrexone over a 28-day period. However,

as the data summarized in Table 8 of Exhibit A shows, the 380 mg dose has an AUC that is at least 3.3 times greater than the AUC of the per day dose of oral regimen of 50 mg per day naltrexone.

Data Analysis

Referring now to Table 8 of the Report shown in Exhibit A, note that the AUC_{0-t} ($AUC_{0-28days}$) for a single dose of MEDISORB® Naltrexone 380 mg on a per day basis can be calculated for Cohort A by dividing the AUC_{0-t} for Cohort A 120.6 by 28 days and for Cohort B, 137.8, by 28 days. For Cohort A, the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} is 4.307 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.278. For Cohort B, the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} is 4.921 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.468. This result was unexpected.

Based on the dose proportionality observed between 190 and 380 mg following a single dose, $AUC_{0-28days}$ for the 190 mg dose may reasonably be predicted to be approximately 2-fold higher than AUC following oral dosing of 50 mg per day for 28 days. This is also evident from Cohort A data showing about a 2-fold higher AUC for MEDISORB® Naltrexone 190 mg. This result was also unexpected.

Cited Reference US Pat No 6,306,425 ("Tice")

I have read the rejections from the Examiner and I have reviewed Tice cited by the Examiner. The Examiner claims that the data found in the table in column 14 of Tice indicates that the F-1' naltrexone-containing injectable formula described also exhibits an AUC which is 3.3 times higher over a period of 32 days as compared to the oral dosing of 50 mg per day of naltrexone for 32 days. This is incorrect.

Tice discloses an injectable formulation containing up to 350 mg of naltrexone. However, Tice does not disclose that the serum AUC of naltrexone is at least about 2 or 3.3 times greater than that achieved by the equivalent 50 mg/day oral administration over

the same period of time. Given that the oral naltrexone is delivered in a daily dose, it is necessary to either extrapolate (or actually measure) the AUC derived from the daily oral dose over the time period in which the AUC of the injectable extended dose is measured, or it is necessary to divide the AUC of the injectable extended dose over the number of days that AUC measurements of the injected extended dose are taken in order to arrive at the daily AUC of the extended dose and thereafter compare that measurement to the daily AUC of the daily oral dose. Therefore what is actually disclosed Tice is that the *extrapolated* 32 day AUC after a single dose of a 50 mg tablet of oral naltrexone (column 15, lines 62-65, 1600 mg naltrexone total dose) is similar to the AUC_{0-32} day after injection of the F-1' naltrexone formulation tested in Tice.

The table in column 15 summarizes the data table in column 14 of Tice which compares the dose delivered in one day (with 50 mg) as compared to the delivery over 32 days. The mean dose is calculated by multiplying the mean daily dose over 32 days (to calculate the dose/day) is 27.8*32=889.6. The F-1' mean over 32 days achieved a 1051.6, which is less than twice the AUC. Looking at the data differently, the AUC over 32 days is 1051.6. The dose per day is 32.8 (1051.6/32 = 32.8), which is not twice 27.8, the per day dose for the 50 mg oral.

Comparison between Tice and the Present Application

Referring now to the graphs of Exhibit C, AUC data for Tice are taken from the text and table in column 14. According to the table, a single oral dose of 50 mg naltrexone was administered, and a mean AUC_{0-24h} value of 27.8 *ug* h/L was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 300 mg injection of naltrexone resulted in a mean AUC_{0-32d} value of 1051.6 *ug* h/L. This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 32.9 *ug* h/L.

AUC data for MEDISORB® Naltrexone are taken from the text and table on page 6 of their clinical study report ALK21-005 (Exhibit B). According to the table on page 6 of

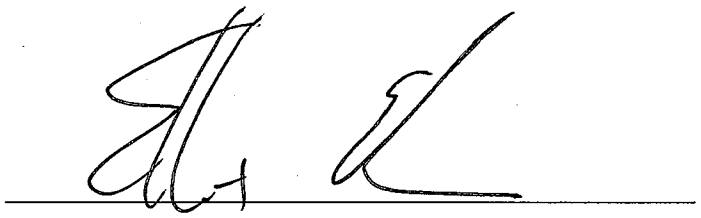
the Report, a single oral dose of 50 mg naltrexone was administered, and a mean $AUC_{0-\infty}$ value of 30.5 *ug* h/L (1.270 ng days/mL) was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 190 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 1722 *ug* h/L (71.75 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 53.8 *ug* h/L. A third set of data indicates that a single 380 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 3444 *ug* h/L (143.5 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 107.6 *ug* h/L.

Comparisons between the graphed data from column 14 of Tice and the data from Exhibit B as shown in Exhibit C indicate that the 50 mg oral doses of Tice and Exhibit B and the single injectable dose of 300 mg of Tice result in similar average daily AUC values of 28-33 *ug* h/L. On the other hand, a single injectable dose of MEDISORB® Naltrexone 190 mg or MEDISORB® Naltrexone 380 mg (Alkermes) result in average daily AUC values that are, respectively, 1.6x (53.8 *ug* h/L) and 3.3x (107.6 *ug* h/L) greater than the average daily AUC value of 32.9 *ug* h/L, obtained from a single injectable dose of 300 mg in accordance with Tice.

Conclusion

Therefore, Tice does not disclose an injectable naltrexone formulation that has the presently claimed AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone. In addition, based on what was known in the prior art including Tice, it was unexpected that an injectable naltrexone formulation such as the MEDISORB® Naltrexone formulation would have an AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Elliot Ehrich

Attachments: Exhibits A, B, C and D

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
Under the paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*)	Docket Number (Optional) 4000.3010 US1
Application Number 11/083,167	Filed March 17, 2005
For Naltrexone Long Acting Formulations and Methods for Use	
Art Unit 1617	Examiner Kendra D. Carter

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$130	$65	$
☑	Two months (37 CFR 1.17(a)(2))	$490	$245	$ 490
☐	Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐	Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐	Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 502807.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 35,729

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Darlene A. Vanstone/	October 5, 2009
Signature	Date
Darlene A. Vanstone	(978) 251-3509
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Table 8 Pharmacokinetic Parameters by Treatment for Naltrexone Following a Single Dose (Cohort A) and Repeat Doses (Cohort B) of Oral Naltrexone (50 mg) and Medisorb Naltrexone (190 and 380 mg) – [Arithmetic Mean (SD)]

COHORT	PARAMETER	ORAL NALTREXONE 50 MG N = 28 (Cohort A) N = 14 (Cohort B)	MEDISORB NALTREXONE 190 MG N = 12	MEDISORB NALTREXONE 380 MG DOSE 1 of 4 N = 12	MEDISORB NALTREXONE 380 MG DOSE 4 of 4 N = 10
A (Single Dose)	C_{max} (ng/mL)	10.64 (6.92)	10.20 (6.67)	12.90 (4.67)	-
	t_{max}[a] (days)	0.04 (0.02-0.08)	2.00 (1.75-24.0)	2.00 (1.50-2.00)	-
	$AUC_{0-\tau}$ (ng*days/mL)	1.278 (0.589)	61.49 (14.78)	120.6 (19.6)	-
	$AUC_{0-\infty}$ (ng*days/mL)	1.270 (0.591)[b]	71.75 (9.06)	143.5 (29.3)	-
	$t_{1/2}$ (days)	0.1611 (0.1065)[b]	7.363 (3.036)	4.948 (1.255)	-
B (Multiple Dose)	$C_{max, ss}$ (ng/mL)	13.70 (10.63)	-	25.03 (12.69)[d]	27.96 (12.17)
	$t_{max, ss}$[a] (days)	0.035 (0.020-0.170)	-	2.00 (1.75-24.0)[e]	2.00 (1.75-3.00)
	$AUC_{0-\tau, ss}$ (ng*days/mL)	1.468 (0.940)	-	137.8 (24.4)[f]	159.9 (24.2)
	$AUC_{0-\infty, ss}$ (ng*days/mL)	1.559 (0.971)[c]	-	-	170.8 (29.6)
	$t_{1/2, ss}$ (days)	0.1683 (0.0687)[c]	-	-	4.732 (1.333)
	$C_{ave, ss}$ (ng/mL)	1.468 (0.940)	-	-	5.712 (0.866)
	$C_{min, ss}$ (ng/mL)	0.05264 (0.10772)	-	-	1.338 (0.946)
	%Fluct (%)	918.0 (222.6)	-	-	466.3 (215.9)
	R	-	-	-	1.127 (0.155)

SD = Standard deviation; %Fluct = Percent fluctuation, calculated as $(C_{max, ss}-C_{min, ss})/ C_{ave, ss}*100$; R = Accumulation ratio, calculated as $AUC_{0-28day, Dose 4, ss}/AUC_{0-28day, Dose 1}$
[a] Presented as median (range); [b] N=27; [c] N=13; [d] C_{max}; [e] t_{max}; [f] $AUC_{0-\tau}$

Source: Appendix 16.7, Table 8 , Table 10 , Table 12 , Table 14 , *and* Table 16 .

EXHIBIT A

CLINICAL STUDY REPORT

1.0 TITLE PAGE

Title:	An Evaluation of the Steady-State and Single-Dose Pharmacokinetics of Medisorb® Naltrexone in Healthy Subjects
Study Number:	ALK21-005
Study Sponsor	Alkermes, Inc. 88 Sidney Street Cambridge, Massachusetts 02139 United States
Date of Report:	Final: 09 November 2004

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EXHIBIT B

Statistical Methods: PK parameters were calculated from plasma concentration of naltrexone and 6ß-naltrexol using noncompartmental techniques. Descriptive statistics of PK parameters are summarized in Section 9.7.2.2.

Analysis of variance (ANOVA) models including treatment or analyte as fixed effects and subject as a random effect were fit to the data and the result was reported for the total population.

Data from subjects who received Medisorb Naltrexone 190 mg and 380 mg in Cohort A were used to assess dose proportionality (AUC and C_{max}) for naltrexone and 6ß-naltrexol. To assess the time invariance of naltrexone and 6ß-naltrexol PK following Medisorb Naltrexone administration, log-transformed AUC and $t_{1/2}$ were compared following single and multiple doses. Accumulation of naltrexone and 6ß-naltrexol following Medisorb Naltrexone administration was assessed by comparing $AUC_{0-\tau, Dose\ 4}$ with $AUC_{0-\tau, Dose\ 1}$ from subjects in Cohort B using a repeated measure ANOVA. Steady state was assessed by examination of the 90% confidence interval (CI) for the slope of the linear regression of log-transformed trough levels versus time. In addition, the theoretical time to steady state (by using the terminal elimination $t_{1/2}$ following a single dose) was also considered. The ratio of 6ß-naltrexol $AUC_{0-\tau}$ to naltrexone $AUC_{0-\infty}$ following oral naltrexone and Medisorb Naltrexone doses was analyzed using a repeated measure ANOVA model.

Descriptive statistics were provided for the appropriate safety parameters, including laboratory assessments and vital signs, by study group.

A secondary post-hoc analysis was performed to explore gender differences in the PK parameters AUC_{0-28} and C_{max} overall in all subjects administered a single Medisorb Naltrexone dose. An ANOVA model including gender was used to determine statistical differences in the overall PK parameters AUC_{0-28} and C_{max} between genders.

A complete description of statistical methods for this study is presented in Section 9.7.

RESULTS

Pharmacokinetics: PK parameters for naltrexone and 6ß-naltrexol following a single dose of oral naltrexone and Medisorb Naltrexone for subjects in Cohort A are presented in the table below:

ANALYTE	PARAMETER	ORAL 50 MG N=28	MEDISORB NALTREXONE 190 MG N=12	MEDISORB NALTREXONE 380 MG N=12
Naltrexone	$AUC_{0-\infty}$ (ng*days/mL)	1.270 (0.591)[a]	71.75 (9.06)	143.5 (29.3)
	C_{max} (ng/mL)	10.64 (6.92)	10.20 (6.67)	12.90 (4.67)
	t_{max} (days)[c]	0.04 (0.02-0.08)	2.00 (1.75-24.0)	2.00 (1.50-2.00)
6ß-naltrexol	$AUC_{0-\infty}$ (ng*days/mL)	35.71 (7.62)	175.4 (26.7)[b]	328.5 (80.2)
	C_{max} (ng/mL)	108.6 (35.6)	14.08 (7.84)	19.43 (6.35)
	t_{max} (days)[c]	0.04 (0.02-0.08)	3.00 (2.00-24.0)	3.00 (2.00-21.0)

Data are presented as arithmetic mean (SD).
[a] N=27; [b] N=10
[c] Presented as median (range).

PK parameters for naltrexone and 6ß-naltrexol following multiple doses of oral naltrexone and Medisorb Naltrexone for subjects in Cohort B are presented in the table below:

ANALYTE	PARAMETER	ORAL 50 MG N=14	MEDISORB NALTREXONE 380 MG Dose 1 of 4 N=12	MEDISORB NALTREXONE 380 MG Dose 4 of 4 N=10
Naltrexone	$AUC_{0-\infty, ss}$ (ng*days/mL)	1.559 (0.971)[a]	-	170.8 (29.6)
	$C_{max, ss}$ (ng/mL)	13.70 (10.63)	25.03 (12.69)[c]	27.96 (12.17)
	$t_{max, ss}$ (days)[b]	0.035 (0.020-0.170)	2.00 (1.75-24.0)[d]	2.00 (1.75-3.00)
6ß-naltrexol	$AUC_{0-\infty, ss}$ (ng*days/mL)	47.20 (14.08)	-	318.3 (80.5)
	$C_{max, ss}$ (ng/mL)	138.7 (36.0)	27.46 (11.78)[c]	34.23 (12.92)
	$t_{max, ss}$ (days)[b]	0.04 (0.02-0.17)	3.00 (3.00-24.0)[d]	3.00 (2.00-3.00)

Data are presented as arithmetic mean (SD).
[a] N=13
[b] Presented as median (range).
[c] $C_{max,}$ [d] t_{max}

Dose-Proportionality: Ratios and 90% CIs for the assessment of dose-proportionality of naltrexone and 6ß-naltrexol PK parameters following a single dose of Medisorb Naltrexone (Cohort A) are presented below.

		GEOMETRIC LS MEANS			
ANALYTE	PARAMETER	MEDISORB NALTREXONE 190 MG	MEDISORB NALTREXONE 380 MG	RATIO[a]	90% CI
Naltrexone	$AUC_{0-\infty}$ (ng*days/mL)	71.3	141	1.975	1.756, 2.222
	C_{max} (ng/mL)	8.34	12.1	1.455	0.991, 2.135
6ß-naltrexol	$AUC_{0-\infty}$ (ng*days/mL)	174	320	1.843	1.590, 2.137
	C_{max} (ng/mL)	11.8	18.4	1.565	1.075, 2.279

[a] Ratio of geometric LS means between the two doses.

Naltrexone and 6ß-naltrexol $AUC_{0-\infty}$ and C_{max} were dose-proportional across the 190 and 380 mg dose range as the 90% CIs for all 4 parameters included the value of 2.

Time invariance: Assessment of time invariance of naltrexone and 6ß-naltrexol PK parameters following Medisorb Naltrexone 380 mg is presented below.

		GEOMETRIC LS MEANS			
ANALYTE	PARAMETER	COHORT A	COHORT B	RATIO[a]	90% CI
Naltrexone	AUC[b]	141	158	1.124	0.982, 1.287
	$t_{1/2}$	4.79	4.56	0.951	0.772, 1.172
6ß-naltrexol	AUC[b]	320	287	0.896	0.754, 1.065
	$t_{1/2}$	5.52	5.02	0.908	0.755, 1.092

Cohort A: Single dose; Cohort B: Multiple dose
[a] Ratio of geometric LS means between cohorts
[b] Calculated as $AUC_{0-\infty}$ (Cohort A)/$AUC_{0-\tau, Dose\ 4}$ (Cohort B).

Naltrexone and 6ß-naltrexol AUC and $t_{1/2}$ did not change with time as the 90% CIs for all 4 parameters included the value of 1.

Accumulation: Assessment of accumulation of naltrexone and 6ß-naltrexol following multiple doses of Medisorb Naltrexone 380 mg (Cohort B) is presented below.

		GEOMETRIC LS MEANS			
ANALYTE	PARAMETER	DOSE 1	DOSE 4	RATIO[a]	90% CI
Naltrexone	$AUC_{0-\tau}$ (ng*days/mL)	136	154	1.134	1.048, 1.226
6ß-naltrexol	$AUC_{0-\tau}$ (ng*days/mL)	255	284	1.114	1.043, 1.191

[a] Ratio of geometric LS means, calculated as $AUC_{0-\tau, Dose\ 4}/AUC_{0-\tau, Dose\ 1}$ (Cohort B).

Naltrexone and 6ß-naltrexol accumulation (13 and 11%, respectively) was not considered clinically relevant.

Steady State: Assessment of steady state of naltrexone and 6ß-naltrexol following multiple doses of Medisorb Naltrexone 380 mg (Cohort B) is presented below.

ANALYTE	SLOPE[a]	90% CI
Naltrexone	-0.001	-0.004, 0.002
6ß-naltrexol	-0.000	-0.004, 0.003

[a] Slope was determined based on the LS mean of log trough levels following doses 1 – 4 in Cohort B

Based on results of the linear regression analysis, both naltrexone and 6ß-naltrexol concentrations reached steady state at the end of the dosing interval following the first dose.

Metabolite:parent AUC Ratio: Assessment of metabolite:parent AUC ratios following oral naltrexone 50 mg and Medisorb Naltrexone 190 mg and 380 mg, are presented below.

		AUC GEOMETRIC LS MEANS (ng*days/mL)			
COHORT	DOSE GROUP	NALTEXONE	6ß-NALTREXOL	Ratio[a]	90% CI
A	Oral (50 mg)	1.16	35.0	30.253	25.969, 35.244
	Medisorb Naltrexone 190 mg	71.3	173	2.432	2.253, 2.626
	Medisorb Naltrexone 380 mg	141	320	2.274	2.117, 2.442
B	Oral (50 mg)	1.24	34.7	28.074	20.752, 37.979
	Medisorb Naltrexone 380 mg	158	287	1.813	1.598, 2.056

[a] $AUC_{0-\infty}$ and $AUC_{0-\tau}$ were used to calculate the ratio and 90% CI following single and multiple doses, respectively.

The metabolite:parent AUC ratio following oral naltrexone administration was approximately 30, whereas, the ratio following Medisorb Naltrexone administration was approximately 2.

Gender Differences: Assessment of gender differences of naltrexone and 6β-naltrexol following a single dose of Medisorb Naltrexone is presented below.

ANALYTE	PARAMETER	RATIO[a]	90% CI[b]
Naltrexone	C_{max} (ng/mL)	0.677	0.469, 0.979
	AUC_{0-28} (ng*days/mL)	1.039	0.823, 1.313
6β-naltrexol	C_{max} (ng/mL)	0.742	0.536, 1.027
	AUC_{0-28} (ng*days/mL)	1.042	0.822, 1.321

[a] The ratio was obtained by exponentiating the difference in the LS means of the natural log-transformed parameters. Presented as Female/Male
[b] 90% CIs for the ratio of Females to Males.

Naltrexone and 6ß-naltrexol C_{max} were lower in females compared with males. Naltrexone and 6ß-naltrexol AUC_{0-28} were similar between females and males following a single dose of Medisorb Naltrexone.

Safety and Tolerability:

No serious adverse events (SAEs) occurred. All AEs were mild in severity, with the exception of 1 event of moderate intensity; no subject experienced a severe AE during the study in any study group.

Oral Naltrexone

Four of the 28 subjects enrolled in Cohort A and 6 of the 14 subjects enrolled in Cohort B reported at least one AE following oral administration. All AEs reported during the oral period were mild in severity and classified as possibly related to study drug by the investigator. The most common AE in Cohort A was dizziness. In Cohort B, nausea and somnolence were the most common AEs.

Medisorb Naltrexone – Cohort A

Two of 12 subjects administered Medisorb Naltrexone 190 mg and 1 of 12 subjects administered Medisorb Naltrexone 380 mg reported at least one AE. All AEs reported for Cohort A were mild in severity and classified as possibly related to study drug by the investigator. No AEs were reported by subjects administered placebo.

Medisorb Naltrexone – Cohort B

Four of 12 subjects administered Medisorb Naltrexone 380 mg reported at least one AE. All AEs reported for Cohort B were mild in severity with the exception of 1 subject who reported diarrhea of moderate severity. The most common AEs in Cohort B were vomiting and dizziness. No AEs were reported by subjects administered placebo.

Three subjects reported injection site reactions (ISRs) following IM administration of Medisorb Naltrexone 380 mg. All ISRs were reported following single dose administration in Cohort A or following Dose 1 in Cohort B. Subject 205-021 reported induration and tenderness; Subject 205-102 reported induration, 1-inch ecchymotic area, tenderness, and redness; and Subject 205-103 reported induration and tenderness. All reported ISRs resolved without sequelae.

There were no trends or clinically meaningful changes from baseline observed in mean or median clinical laboratory values or vital signs for any of the study groups.

There were no trends or clinically meaningful changes observed in ECG values for subjects in this study. QTcB and QTcF interval data were comparable for all dose groups. There was no evidence of an effect on cardiac conduction as detailed by the 12-lead ECG intervals duration.

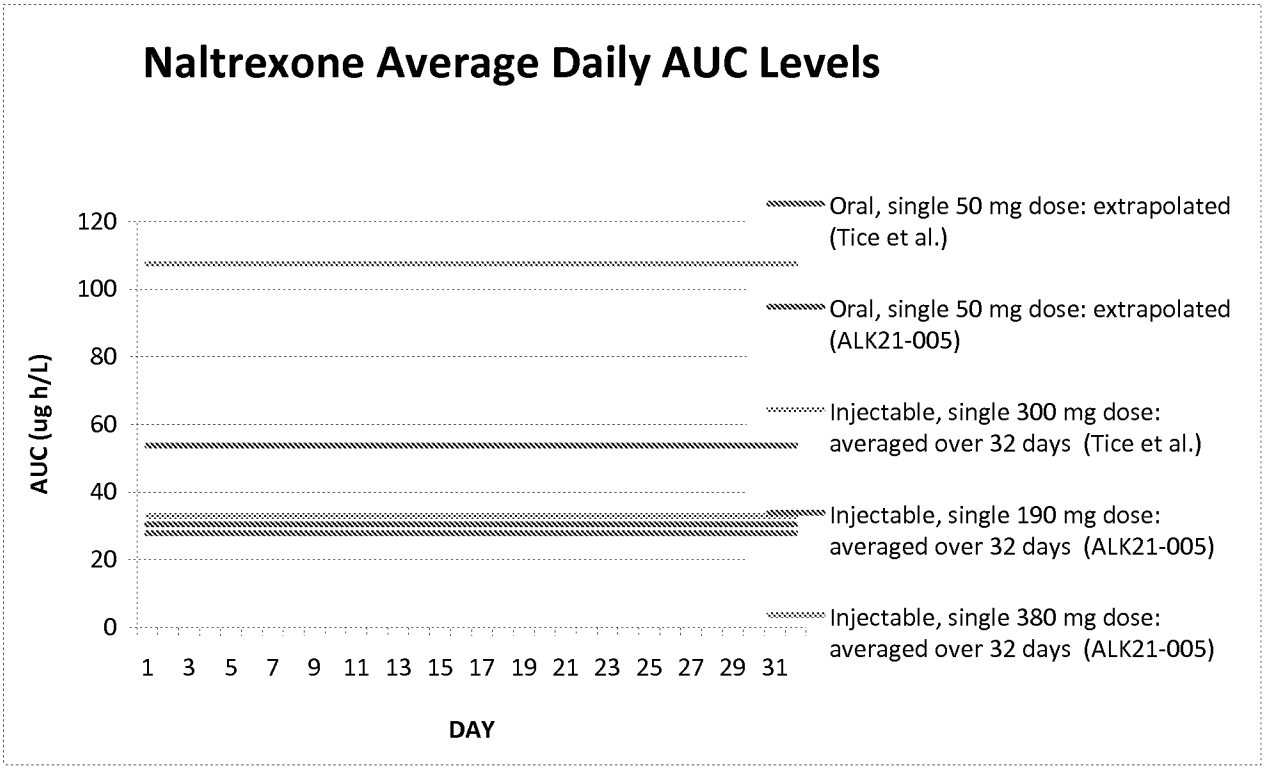
Efficacy:

No efficacy parameters were evaluated during this clinical trial.

Conclusions:	▪ Naltrexone and 6ß-naltrexol $AUC_{0-\infty}$ and C_{max} were dose-proportional following single administration of Medisorb Naltrexone across the 190 to 380 mg dose range. ▪ Based on time invariance analysis of AUC and $t_{1/2}$, the PK of naltrexone and 6ß-naltrexol was similar between single and multiple doses of Medisorb Naltrexone 380 mg. ▪ Accumulation of naltrexone and 6ß-naltrexol was 13 and 11%, respectively, following multiple doses of Medisorb Naltrexone. ▪ Steady state was reached for naltrexone and 6ß-naltrexol at the end of the dosing interval following the first dose of Medisorb Naltrexone 380 mg. ▪ The metabolite:parent AUC ratios following Medisorb Naltrexone and oral administration were approximately 2 and 30, respectively. Overall, naltrexone exposure following Medisorb Naltrexone was higher and 6ß-naltrexol exposure was lower following Medisorb Naltrexone 380 mg administration compared with the oral naltrexone 50 mg administration. ▪ Naltrexone C_{max} was approximately 1/3 lower in females compared with males, however, overall exposure (AUC) was similar between males and females. ▪ Single and multiple doses of Medisorb Naltrexone were well tolerated based on the number and severity of reported AEs. There were no trends or clinically meaningful changes from baseline observed in mean or median clinical laboratory values or vital sign findings for any of the study groups. ▪ There were no trends or clinically meaningful changes observed in ECG values for subjects in this study. There was no evidence of an effect on cardiac conduction as detailed by the 12-lead ECG intervals duration
GCP Compliance:	Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The Alkermes commitment is compliance with this standard to provide assurance that the rights, safety, and well-being of trial subjects will be protected, consistent with the principles that have their origin in the Declaration of Helsinki.
Date of the Report:	Final: 09 November 2004

	AUC ug h/L				
	Oral		**Injectable**		
	50mg	50mg	300mg	190mg	380mg
DAY	Tice et al	ALK21-005	Tice et al	ALK21-005	ALK21-005
1	27.8	30.5	32.9	53.8	107.6
2	27.8	30.5	32.9	53.8	107.6
3	27.8	30.5	32.9	53.8	107.6
4	27.8	30.5	32.9	53.8	107.6
5	27.8	30.5	32.9	53.8	107.6
6	27.8	30.5	32.9	53.8	107.6
7	27.8	30.5	32.9	53.8	107.6
8	27.8	30.5	32.9	53.8	107.6
9	27.8	30.5	32.9	53.8	107.6
10	27.8	30.5	32.9	53.8	107.6
11	27.8	30.5	32.9	53.8	107.6
12	27.8	30.5	32.9	53.8	107.6
13	27.8	30.5	32.9	53.8	107.6
14	27.8	30.5	32.9	53.8	107.6
15	27.8	30.5	32.9	53.8	107.6
16	27.8	30.5	32.9	53.8	107.6
17	27.8	30.5	32.9	53.8	107.6
18	27.8	30.5	32.9	53.8	107.6
19	27.8	30.5	32.9	53.8	107.6
20	27.8	30.5	32.9	53.8	107.6
21	27.8	30.5	32.9	53.8	107.6
22	27.8	30.5	32.9	53.8	107.6
23	27.8	30.5	32.9	53.8	107.6
24	27.8	30.5	32.9	53.8	107.6
25	27.8	30.5	32.9	53.8	107.6
26	27.8	30.5	32.9	53.8	107.6
27	27.8	30.5	32.9	53.8	107.6
28	27.8	30.5	32.9	53.8	107.6
29	27.8	30.5	32.9	53.8	107.6
30	27.8	30.5	32.9	53.8	107.6
31	27.8	30.5	32.9	53.8	107.6
32	27.8	30.5	32.9	53.8	107.6

EXHIBIT C


Naltrexone Average Daily AUC Levels
AUC (ug h/L)
120
100
80
60
40
20
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
DAY
Oral, single 50 mg dose: extrapolated (Tice et al.)
Oral, single 50 mg dose: extrapolated (ALK21-005)
Injectable, single 300 mg dose: averaged over 32 days (Tice et al.)
Injectable, single 190 mg dose: averaged over 32 days (ALK21-005)
Injectable, single 380 mg dose: averaged over 32 days (ALK21-005)

Elliot W. Ehrich, MD

Senior Vice President, Research and Development
Chief Medical Officer
Alkermes, Inc.

Work:
88 Sidney Street
Cambridge MA, 02139
Phone 617 583 6190
elliot.ehrich@alkermes.com
www.alkermes.com

Home:
2 Oak Meadow Rd.
Lincoln, MA 01773
781 259 4470

- Senior Vice President
  Research and Development, Chief Medical Officer 2007-Present
- Executive Officer 2006-Present
- Vice President, Science and Development, Chief Medical Officer 2003-2007
- Vice President, Medical Affairs 2000-2003

PRIOR EMPLOYMENT

Merck & Co., Inc. 1993-2000

- Senior Director, Clinical Research, Pulmonary-Immunology 1998 - 2000
- Director, Clinical Research, Pulmonary-Immunology 1995 - 1998
- Associate Director, Clinical Pharmacology 1993 –1995

EDUCATION

SCHOOL	DATE	MAJOR	DEGREE
Princeton University Princeton, NJ	1977 - 1981	Biochemistry	B.A., *Magna cum Laude, Phi Beta Kappa*
Columbia University College of Physicians and Surgeons, New York, NY	1982 - 1986	Medicine	M.D.

EXHIBIT D

POSTGRADUATE TRAINING

Stanford University, Stanford, CA 1986 - 1993

Internship and Residency, Department of Medicine
Clinical Fellowship, Rheumatology, Division of Immunology and Rheumatology
Cancer Research Institute/FW. Kirby Foundation Postdoctoral Fellowship 1990-1993,
Laboratory of Dr. Mark Davis, HHMI, Department of Microbiology and Immunology

European Molecular Biology Laboratory (EMBL) 1981, 1985
Heidelberg, Germany, Research Associate, Laboratory Dr. Hans Lehrach

ACADEMIC APPOINTMENT

Clinical Assistant Professor of Medicine 1997-Present
Robert Wood Johnson Medical School

PROFESSIONAL HONORS

Fellow, American College of Rheumatology 1993 - Present
American College of Rheumatology Senior Rheumatology Scholar Award
Board Certification, Rheumatology, American Board of Internal Medicine 1993-2003
Board Certification, Internal Medicine, American Board of Internal Medicine 1989-Present
Board Certification, National Board of Medical Examiners 1986-Present

PUBLICATIONS

A Poustka, T Pohl, D Barlow, G Zehetner, A Craig, F Michiels, E Ehrich, A-M Frischauf, and H Lehrach (1986): Molecular Approaches to Mammalian Genetics, *Cold Spring Harbor Symposium on Quantitative Biology*, 51:131-139.

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Electronic Patent Application Fee Transmittal

Application Number:	11083167
Filing Date:	17-Mar-2005
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Filer:	Darlene Vanstone/Hollie Wakefield
Attorney Docket Number:	4000.3010 US1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1253	1	490	490

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**490**

Electronic Acknowledgement Receipt

EFS ID:	6200582
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Hollie Wakefield
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	05-OCT-2009
Filing Date:	17-MAR-2005
Time Stamp:	13:23:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$490
RAM confirmation Number	8162
Deposit Account	502807
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment Copy Claims/Response to Suggested Claims	Amendment.pdf	101259 1e634198c745bb8a7ae72b71e524d588834fa9c4	no	9
Warnings:					
Information:					
2	Oath or Declaration filed	Dec1132.pdf	219788 4e74c6c74b78ee8a5dccfe1558dccadb7301bda1	no	5
Warnings:					
Information:					
3	Extension of Time	ExtTime.pdf	43485 dc07b92be9168c6ec853732cf758cd57443d3c53	no	1
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Information:					
4	Miscellaneous Incoming Letter	ExhibitA.pdf	599891 76f0850413f3285207d3aa1c00c768e4c7a228e3	no	1
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Information:					
5	Miscellaneous Incoming Letter	ExhibitB.pdf	3375176 4f99b5c3da121ee6095ba6fca00bd6d8f07caa41	no	6
Warnings:					
Information:					
6	Miscellaneous Incoming Letter	ExhibitC.pdf	75215 1ad05cfd1c44be51a43c86cd007a99534fa8729d	no	2
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	ExhibitD.pdf	40927 672771ce5eaafe70570954ba7c4752267dec43db	no	4
Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	30281 46d666f060d9fa519156daa4f153fe4c505dcd9a	no	2
Warnings:					
Information:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/083,167	03/17/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/05/2009

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 23	Minus	** 47	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LAMONT MCLAUCHLIN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/08a (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11083167
Filing Date	2005-03-17
First Named Inventor	Elliot Ehrich
Art Unit	1617
Examiner Name	Kendra D. Carter
Attorney Docket Number	4000.3010 US1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20040151774	A1	2004-08-05	Pauletti et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11083167
	Filing Date	2005-03-17
	First Named Inventor	Elliot Ehrich
	Art Unit	1617
	Examiner Name	Kendra D. Carter
	Attorney Docket Number	4000.3010 US1

	1		☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11083167
	Filing Date	2005-03-17
	First Named Inventor	Elliot Ehrich
	Art Unit	1617
	Examiner Name	Kendra D. Carter
	Attorney Docket Number	4000.3010 US1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Darlene A. Vanstone/	Date (YYYY-MM-DD)	2009-08-05
Name/Print	Darlene A. Vanstone	Registration Number	35729

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich

Application No.: 11/083,167 Group Art Unit: 1617

Filed: March 17, 2005 Examiner: Kendra D. Carter

Confirmation No.: 8002

Title: Naltrexone Long Acting Formulations and Methods of Use

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Supplemental Information Disclosure Statement is submitted:

[ ] under 37 CFR 1.129(a), or
(First/Second submission after Final Rejection)

[ ] under 37 CFR 1.97(b), or
(Within any one of the following time periods: three months of filing national application (other than a CPA) or date of entry of the national stage in an international application; or before the mailing date of a first office action on the merits in a non-provisional application, including a CPA, or a Request for Continued Examination).

[X] under 37 CFR 1.97(c) together with either:
[X] a Statement under 37 CFR 1.97(e), as checked below, or
[ ] a $180.00 fee under 37 CFR 1.17(p), or
(After the 37 CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)

[ ] under 37 CFR.1.97(d) together with:
[ ] a Statement under 37 CFR 1.97(e), as checked below, and
[ ] a $180.00 fee under 37 CFR 1.17(p), or
(Filed after final action or notice of allowance, whichever occurs first, but on or before payment of the issue fee)

[ ] under 37 CFR 1.97(i):
Applicant requests that the IDS and cited reference(s) be placed in the application filewrapper. (Filed after payment of issue fee)

Statement Under 37 CFR 1.97(e)

[X] Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

[ ] No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)
(Applies to original applications (other than design) filed on or after May 29, 2000)

[X] Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in -§ 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

[X] Enclosed herewith is form PTO-1449:

[ ] Copies of the cited references **(** **)** are enclosed.

[X] Since this application was filed after June 30, 2003, copies of issued U.S. patents and published U.S. applications are not required and are not being provided.

[ ] Copies of cited references are enclosed except those entered in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed. [The earlier application contains copies of the cited references.]

[ ] The listed references **(** **)** were cited in the enclosed International Search Report in a counterpart foreign application.

[ ] The "concise explanation" requirement (non-English references) for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

[ ] the explanation provided on the attached sheet.
[ ] the explanation provided in the Specification.
[ ] submission of the enclosed International Search Report.
[ ] submission of the enclosed English-language version of a foreign Search Report and/or foreign Office Action.
[ ] the enclosed English language abstract.

It is requested that the information disclosed herein be made of record in this application.

Method of payment:

[ ] A check for the fee noted above is enclosed, or the fee has been included in the check with the accompanying Reply. A copy of this Statement is enclosed.
[ ] Please charge Deposit Account 502807 in the amount of [$]. A copy of this Statement is enclosed.
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Respectfully submitted,

ELMORE PATENT LAW GROUP, P.C.

/Darlene A. Vanstone/

By _____
Darlene A. Vanstone
Registration No.: 35,729
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Dated: **June 22, 2009**

Electronic Acknowledgement Receipt

EFS ID:	5563598
Application Number:	11083167
International Application Number:	
Confirmation Number:	8002
Title of Invention:	Naltrexone long acting formulations and methods of use
First Named Inventor/Applicant Name:	Elliot Ehrich
Customer Number:	38421
Filer:	Darlene Vanstone/Hollie Wakefield
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	22-JUN-2009
Filing Date:	17-MAR-2005
Time Stamp:	17:20:46
Application Type:	Utility under 35 USC 111(a)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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2	Transmittal Letter	IDSLET.pdf	78385 e414bcde71f89c54e0b243b48349de2bb9ab14d2	no	3
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<u>New Applications Under 35 U.S.C. 111</u>
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<u>National Stage of an International Application under 35 U.S.C. 371</u>
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<u>New International Application Filed with the USPTO as a Receiving Office</u>
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