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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 05/05/2009

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

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/05/2009	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	1617	

-- 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 *20 March 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* 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4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.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 and 6-23* 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 *8/29/05;12/01/05;6/23/08;7/9/08;7/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 2, and 6-23 in the reply filed on March 20, 2009 is acknowledged. The traversal is on the ground(s) that Group I and Group II are not mutually exclusive. One could administer the long acting naltrexone of Group I to an individual in accordance with the method of Group II and achieve the serum AUC levels of naltrexone of Group I. This is not found persuasive because the method of Group I does not require the specific method step of treating alcohol and specific days in which the individual should or should not abstain from alcohol. Thus, claims 3-5 are withdrawn from consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

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

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claims 6, 18, 20 and 22, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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).

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. 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; addresses claims 1, 7, 8 and 14-17). 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 more than 3.3 times greater than that achieved by 50 mg/day oral administration (see column 14, lines 40-55; addresses claim 1). Naltrexone is employed in an amount in the range of 15 to 50 weight % (see claim 1; addresses claim 23).

In regards to claims 6 and 19, in which the individual has not used oral naltrexone before administration, Tice et al. teach that the primary application for the subject formulations is as an intramuscular injection (see column 5, lines 52-23). Further the invention is designed to avoid oral administration such that compliance of taking medication is achieved (see column 16, lines 55-60).

In regards to claim 13, Tice et al. teaches the limitation in which the amount of naltrexone is about 380 mg, because the Examiner reads the about 350 mg of naltrexone that Tice et al. teaches (see column 4, lines 36-38) reads on about 380 mg.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 22 is rejected under 35 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 teachings of Tice et al. are as those applied to claims 1, 2, 6-21 and 23 above.

Tice et al. does not teach a polylactide-co-glycolide polymer.

Chadrashekar et al. teach a controlled release liquid delivery compositions of active compounds such as naltrexone with polymers such as polylactides and poly(lactide-co-glycollide) as the controlled release additive (see abstract; claims 1 and 2; column 7, line 15).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Tice et al. and a polylactide-co-glycolide polymer because it is known in the art that these type of polymers are known to provide controlled release of active ingredients. Since Tice et al. teaches a polylactide as the controlled release additive, it is obvious for one skilled in the art to

use other equivalents such as polylactide-co-glycolide polymers as demonstrated by Chadrashekar et al.

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 7:30 am - 4:00 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 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 11/083,167	Applicant(s)/Patent Under Reexamination EHRICH, ELLIOT	
	Examiner KENDRA D. CARTER	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,143,314	11-2000	Chandrashekar et al.	424/426
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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							
	1	÷	✓							
	2	÷	✓							
	3	÷	N							
	4	÷	N							
	5	÷	N							
	6	÷	✓							
	7	÷	✓							
	8	÷	✓							
	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12	÷	✓							
	13	÷	✓							
	14	÷	✓							
	15	÷	✓							
	16	÷	✓							
	17	÷	✓							
	18	÷	✓							
	19	÷	✓							
	20	÷	✓							
	21	÷	✓							
	22	÷	✓							
	23	÷	✓							
	24	-	-							
	25	-	-							

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

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	3615	naltrexone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:29
L6	2233	l5 and injection	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L7	1289	l6 and (sustained depot)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L8	2833	naltrexone and (parenter$ or injection or intramuscul$ or subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L9	996	L8 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L10	412	L9 and sustained	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L11	412	L10 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:30
L12	996	L8 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:31
L13	319	L7 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:31
L14	170	l13 and (week month)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:32

L15	138	l14 and (intramuscular$ subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:33
L16	11	l5 near (high near dose)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 11:57
L17	2557	l5 and alcohol	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:01
L18	299	L17 and @py<"2000"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:01
L19	206	l18 and (intramuscular$ subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:02
L20	79	l19 and week	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:02
L21	410	L8 and @py<"2000"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:06
L22	102	l21 and ("500" near mg)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:06
L23	10	L5 and @py<"1980"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:24
L24	144	L5 and @py<"1990"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:26
L25	84	l24 and (parenter$ or injection or intramuscul$ or subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:27
L26	27	"6306425"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 12:43

L27	48	"4882335"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 14:54
L28	14	l5 and (polylactide near glycolide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 14:55
L29	8	US-4882335-$.DID. OR US-6264987-$.DID. OR US-5654008-$.DID. OR US-5792477-$.DID. OR US-6358443-$.DID. OR US-6306425-$.DID. OR US-5407609-$.DID. OR US-4719219-$.DID.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/04/29 15:20
L30	33	"5512593"	US-PGPUB; USPAT; USOCR	OR	OFF	2009/04/29 15:21
L31	0	l29 and (polylactide near glycolide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 15:22
L32	5	l29 and glycolide	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/04/29 15:22
S1	307	naltrexone and AUC	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 18:52
S2	64	S1 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 18:53
S3	46	S2 and parenter$	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 18:56
S4	62	S2 and (parenter$ or injection or intramuscul$ or subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 18:58

S5	2719	naltrexone and (parenter$ or injection or intramuscul$ or subcutaneous$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 19:01
S6	996	S5 and @py<"2004"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 19:01
S7	412	S6 and sustained	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 19:03
S8	299	S7 and alcohol	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 19:04
S9	38	S7 and AUC	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/02/04 19:39

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(**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	
Attorney Docket Number	4000.3010 US1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	
	Attorney Docket Number	4000.3010 US1

/K.C./	1	O'MALLEY, Stephanie S. et al., "Initial and Maintenance Naltrexone Treatment for Alcohol Dependence Using Primary Care vs Specialty Care. A Nested Sequence of 3 Randomized Trials," ARCH INTERN MED., 163: 1695-1704 (2003).	☐
/K.C./	2	LATT, Noeline C. et al., "Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting," MJA, 176: 530-534 (2002).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Kendra Carter/	Date Considered	04/29/2009

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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]

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	First Named Inventor	Elliot Ehrich
	Art Unit	1617
	Examiner Name	
	Attorney Docket Number	4000.3010 US1

/K.C./	1	HEINALA, Pekka et al., "Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial," J Clinical Psychopharmacology, 21(3):287-292 (2001).	☐
/K.C./	2	"Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)," Addiction Treatment Forum, Ed., LEAVITT, Stewart, pp. 1-8 (2002).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Kendra Carter/	Date Considered	04/29/2009

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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	
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
/K.C./	1	6495155	B1	2002-12-17	Tice, et al.	

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					

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]
/K.C./	1	01/43726	WO	A	2001-06-21	Trident Tech LLC		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

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	
	Attorney Docket Number	4000.3010 US1

/K.C./	1	Reuning, R.H., et al., "Pharmacokinetic quantitation of naltrexone release from several sustained-released delivery," NIDA. Research Monograph, Institute on Drug Abuse, 28:172-184, (1981).	☐
/K.C./	2	Yolles, S., et al., "Long acting delivery for narcotic antagonists II: release reates of naltrexone from Poly(lactic acid) composites," PDA J. of Pharm. Sci and Tech., 64(2):348-349, (1995)	☐

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	04/29/2009

*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.

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
/K.C./	AA	4,882,335	11-21-1989	Sinclair
/K.C./	AB	6,264,987	07-24-2001	Wright *et al.*
/K.C./	AC	5,654,008	08-05-1997	Herbert *et al.*
/K.C./	AD	5,792,477	08-11-1998	Rickey *et al.*
/K.C./	AE	6,358,443	03-19-2002	Herbert *et al.*
/K.C./	AF	6,306,425	10-23-2001	Tice *et al.*
/K.C./	AG	5,407,609	04-18-1995	Tice *et al.*
/K.C./	AH	4,719,219	01-12-1988	Arvidsson *et al.*
/K.C./	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
/K.C./	BA	60/554,658	03-19-2004	Elliott Ehrich, *et al.*
/K.C./	BB	60/554,785	03-19-2004	Elliott Ehrich, *et al.*
/K.C./	BC	11/082,420	03-17-2005	Elliott Ehrich, *et al.*
/K.C./	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
/K.C./	AL	WO 2004/108084 A2	12-16-2004	Alkermes Controlled Therapeutics, II		
/K.C./	AM	WO 2004/064752 A2	08-05-2004	Alkermes Controlled Therapeutics, Inc.		

EXAMINER	DATE CONSIDERED

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 JC56 AUG 29 2005 PATENT & TRADEMARK OFFICE

		OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*
/K.C./	AR	Swift, Robert M., "Drug Therapy for Alcohol Dependence," *New England J. of Med., 340*(19): 1482-1490 (1999).
/K.C./	AS	Karam-Hage, Maher and Brower, Kirk J., "Gabapentin Treatment for Insomnia Associated With Alcohol Dependence," *Am. J. Psychiatry, 157*(1): 151-153 (2000).
/K.C./	AT	Myrick, M.D., Hugh, *et al.*, "Gabapentin Treatment of Alcohol Withdrawal," *Am. J. of Psychiatry, 155*(11): 1626-1627
/K.C./	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.
/K.C./	AV	Swift, R., *et al.*, "Naltrexone Effects on Diazepam Intoxication and Pharmacokinetics in Humans," *Psychopharmacology, 135*(3): 256-262 (1998), Abstract Only.
/K.C./	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.
/K.C./	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.
/K.C./	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.
/K.C./	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.
/K.C./	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	DATE CONSIDERED
/Kendra Carter/	04/29/2009

PTO-1449 REPRODUCED	ATTORNEY DOCKET NO.	APPLICATION NO.	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION	4000.3010 US1	11/083,167	
	APPLICANT		
	Elliot Ehrich		
December 1, 2005	FILING DATE	CONFIRMATION NO.	GROUP
(Use several sheets if necessary)	March 17, 2005	8002	1614

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*		
/K.C./	DA	Bartus, *et al.*, Vivitrex®, an Injectable, Extended-Release Formulation of Naltrexone, Provides Pharmacokinetic and Pharmacodynamic Evidence of Efficacy for 1 Month in Rats," *Neuropsychopharmacology*, 28:1973-1982 (August 2003).

EXAMINER	DATE CONSIDERED
/Kendra Carter/	04/29/2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	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

REPLY TO RESTRICTION REQUIREMENT

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

Sir:

This Restriction Requirement is being filed in response to the Office Action Summary mailed from the U.S. Patent and Trademark Office on February 20, 2009, in the above-identified application.

Remarks/Arguments begin on page **2** of this paper.

REMARKS

In the restriction requirement, the Examiner has required restriction to one of the following inventions under 35 U.S.C. §121.

I. Claims 1, 2 and 6-23, are 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 two times, preferable at least about three times greater than that achieved by 50 mg/day oral administration, classified in class 514, subclass 468 and 281 for example.

II. Claims 3-5, are drawn to a method of treating an individual in need of naltrexone comprising administering naltrexone, in the absence of coadministering alcohol, to an individual who has not undergone alcohol abstinence, classified in class 514, subclass 468,281 and 811 for example.

Applicants elect Group I, claims 1, 2 and 6-23 with traverse. Applicant's grounds for traversal are set forth below.

The Examiner asserts that the inventions of Group I and Group II are distinct because the inventions as claimed have different design, effect and function citing MPEP §806.05(j). The Examiner asserts that the method of Group I requires a specific serum AUC and dosage, while the method of Group II is to treat alcohol addiction with a specific method.

The methods of Group I and Group II are not mutually exclusive. One could administer the long acting naltrexone of Group I to an individual in accordance with the method of Group II and achieve the serum AUC levels of naltrexone of Group I.

The subject matter of Groups I and II are not so different in design, effect and function as to justify restriction. To be clear, Applicants are not making any admissions in this response with regard to whether or not the methods of Group I and II are patentably distinct. Applicants are merely pointing out that the differences between the inventions do not justify restriction under the patent law in the same way that the differences between an article of clothing and a locomotive bearing may justify restriction as is exemplified in MPEP §806.06.

In addition, the Examiner has not provided a single technical reason to support restriction. The Examiner has not provided any evidence that the inventions have achieved a separate status in the art in view of their differing classification or due to recognized divergent subject matter. In fact, the class and subclasses appear to be the same according to the Examiner. The Examiner has also not provided any evidence that there would be any issues with the prior art relating to one Group and not the other.

The fundamental and equitable purpose of the test for restriction is where a burden in examining the whole exists. The Examiner has not shown such a burden to exist in the examination of Groups I and II together. The restriction is therefore improper.

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: **March 20, 2009**

Electronic Acknowledgement Receipt

EFS ID:	5006534
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-MAR-2009
Filing Date:	17-MAR-2005
Time Stamp:	15:21:12
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	Response to Election / Restriction Filed	20090320RestrictionReqFILED.pdf	66685 6ab4b1d2830160a64aaef07513163268834 60caf	no	4

Warnings:	
Information:	

Total Files Size (in bytes):	66685

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
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 02/20/2009

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

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
02/20/2009	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	1617	

-- 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 *1* 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 September 2007*.

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* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-23* 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2 and 6-23, are 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 two times, preferable at least about three times greater than that achieved by 50 mg/day oral administration, classified in class 514, subclass 468 and 281 for example.

II. Claims 3-5, are drawn to 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, classified in class 514, subclass 468, 281 and 811 for example.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and Group II are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant

case, the inventions as claimed have different design, effect and function. Particularly, the method of Group I requires a specific serum AUC and dosage. On the other hand, Group II is to treat alcohol addiction with a specific method.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement

may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

A telephone call was made to Carylyn Elmore on February 10, 2009 to request an oral election to the above restriction requirement, but the Applicant requested a written restriction.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

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 7:30 am - 4:00 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 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

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								
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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: Not Yet Assigned

Confirmation No.: 8002

Title: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

4th 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)

[X] 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).

[ ] under 37 CFR 1.97(c) together with either:
- [ ] 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)

[ ] 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:

[**X**] 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.]

[**X**] The listed references were cited in the attached Supplementary European 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.

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Respectfully submitted,

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(54) Title: SYSTEM AND METHOD FOR EXTENDED DELIVERY OF A THERAPEUTIC AGENT WITH ITS RECEPTOR LOADING DOSE

(57) Abstract: The present invention provides systems and methods for administering a therapeutic agent to a patient in need an initial loading dose of the therapeutic agent administered in conjunction with long-term maintenance dose of the therapeutic agent. The present invention discloses subcutaneous-implantable dosage forms capable of administering the long-term maintenance dose of the therapeutic agent in a steady state or zero order manner. Systems and methods for administering an initial loading dose of a therapeutic agent administered in conjunction with an extended release dosage form of the therapeutic agent, and optionally in conjunction with a receptor loading dose of the therapeutic agent, are useful in the treatment of various diseases and disorders.

SYSTEM AND METHOD FOR EXTENDED DELIVERY OF A THERAPEUTIC AGENT WITH ITS RECEPTOR LOADING DOSE

Technical Field

The present invention relates to a system and method for administering a therapeutic agent to a patient in need of such agent over an extended period of time in conjunction with an initial loading dose of a therapeutic agent. Specifically, the system and method of the present invention utilize at least one non-erodible, subcutaneous-implantable dosage form for administering the therapeutic agent over an extended period of time while the initial loading dose may be administered by any method known in the art of drug delivery. Advantageously, the non-erodible, subcutaneous-implantable dosage forms of the present invention provide a steady state or zero order release of the therapeutic agent over the lifetime of the subcutaneous-implantable dosage form thereby decreasing the number of times that the patient needs to be seen by a healthcare provider and increasing patient compliance for long-term therapeutic regimens. Diseases/disorders which may be beneficially treated by the system and method of the present invention include, but are not limited to the following: addictive disorders; psychiatric disorders; infectious diseases; cardiovascular diseases; respiratory diseases; inflammatory conditions; immune-based diseases; auto-immune diseases; bone diseases; and cancers.

Background of the Invention

Patient compliance is one of the most important aspects to disease/disorder treatment facing healthcare providers in their efforts to treat diseases/disorders that require an initial loading dose of a therapeutic agent followed by a long-term therapeutic regimen. In the past, healthcare providers have had to rely upon patients taking their medicine without supervision or in extreme cases healthcare providers have had to visit patients in their homes to supervise that the patients have taken their medicine. Long-term management of therapeutic regimens is therefore a burden on both the patient and the healthcare provider,

which requires frequent trips/visits for the patient, frequent administration of the therapeutic agent and frequent refills of the therapeutic agent, resulting in high cost to the patient and healthcare provider. Thus, patient compliance in long-term therapeutic regimens is the weak link in treating diseases/disorders that can be eradicated or controlled by long-term therapeutic administration.

Additionally, several diseases/disorders that may be effectively treated through the use of long-term administration of a therapeutic agent will benefit from an initial loading dose of the therapeutic agent administered concurrently with the long-term therapy. In particular, addictive disorders will benefit from such a combination. The initial loading dose can serve to help the patient overcome the initial withdrawal symptoms, which can be quite severe, and the long-term therapy will held to keep the recovering patient from reverting to drug use.

In particular, the long-term treatment of patients addicted to narcotics is a pressing healthcare concern. Addiction to heroin and other narcotics is a serious healthcare problem in the United States. Federal figures in 1998 estimate that there are more than 800,000 opioid addicts in the United States, and this number appears to be growing (McCaffery, B., Publications of the Department of Justice, U.S. Navy, 1993, 3). Current methods of treating narcotic addiction can be divided into two groups: (1) opiate agonist treatment (replacing the narcotic that an addict has been using with a medically sanctioned, safer narcotic) and (2) "drug-free," non-agonist treatment. Narcotic antagonists (also known as narcotic receptor blockers), discussed later, have been used to improve the outcome of the second type of treatment.

Narcotic or opiate agonists used in the treatment of narcotic addiction include methadone, LAAM (L-Alpha-Acetyl-Methadol), and most recently buprenorphine. Methadone was first described by Dole and Nyswander in 1965 as a method of helping heroin addicts to decrease their use, thereby decreasing crime and other costs to society associated with heroin use. Today in the United States, it is estimated that there are 112,000 patients on methadone maintenance. LAAM, and more recently, buprenorphine, have been studied as narcotic substitutes for treating narcotics addiction. These substitutes have been effective at meeting their stated goals, including decreasing heroin use and decreasing crime and the spread of HIV and other infections associated with drug use. Many physicians, patients, and

members of the general public, however, find the approach of substituting other addictive narcotics for heroin to be a less than ideal form of long-term treatment.

Drug-free treatment programs are found throughout the United States and represent the most common form of treatment for addiction. After detoxification, the patient is provided with counseling in the form of either individual or group therapy. The patient is usually expected to make a commitment to avoid alcohol and other mood altering drugs, and to attend Narcotics Anonymous meetings or other 12-step support groups. Sometimes the patient is housed in a supervised recovery residence or therapeutic community to enhance recovery rates. Even with this intensity of treatment, however, long-term recovery success rates are low and relapse is altogether common.

Narcotic antagonists (naltrexone, naloxone, cyclazocine, and nalmefene) have been used since 1978 to try to enhance the success rates of drug-free treatment programs. These compounds work by blocking the opiate receptors for narcotics in the brain, thereby preventing the patient from feeling any of the effects of the narcotic if the patient relapses back to narcotic use. When faithfully administered, narcotic antagonists are extremely effective in preventing relapse and treating narcotics addiction.

The most commonly used drug in this category is naltrexone, which is approved by the FDA in the oral dosage form for use as a narcotic antagonist. When the recommended dose of 50mg is taken orally, it provides complete blockage for 24 hours. It can be administered three times per week to ensure the patient's compliance with drug-free treatment. Studies have confirmed naltrexone's effectiveness, especially when patients are subject to court ordered treatment, or in other similar situations in which the addict is highly motivated (Tai, et al. NIDA Treatment Workshop "Nalterxone - An Antagonist Therapy for Heroin Addiction", November 12-13, 1997). However, in real world settings, naltrexone's effectiveness is very low. Involuntary or purposeful non-compliance with self-administration by patients has limited the utility of orally administered naltrexone. Accordingly, the drug has been used infrequently in most treatment settings.

To increase the effectiveness of narcotic antagonists, a number of delivery systems have been tried:

1. Naltrexone pellets - Gooberman and Malmberg have developed an implanted pellet that contains 1 gm of naltrexone ("Depot Naltrexone Implants for Opiate Dependence: Clinical Experience, Plasma Levels, Opiate Challenge Results in over 200

Patients", International Council on Alcoholism and Addiction Annual Meeting, Cairo, May 17-22, 1997). It provides the naltrexone in a tightly compressed pellet, which is inserted under the skin and slowly releases the drug over a 40-80 day period. The release rate has not been well established but it appears to be inefficient and to vary widely between patients. It is not an FDA-approved product. One of the problems with this delivery system is that the pellets tend to liquefy towards the end of their lifespan, making removal all but impossible. Moreover, being a first order release system, it is unlikely that the pellet will be able to release naltrexone over an extended period of time without creating a significant risk of toxicity because of the high initial levels that would be required. With a first order release system, the only way to increase the duration of the effect is to increase the total dose and accordingly, the size of the pellet. A dose higher than 1000 mg poses a number of problems. First, there is a greater risk of toxicity if the pellet disintegrates. Second, a bigger pellet presents a significant challenge to subcutaneous insertion and acceptance by patients.

2. Naltrexone microspheres - In this system, microspheres containing naltrexone are injected into patients intramuscularly. They were originally developed through the National Institute of Drug Abuse (NIDA) around 1970 and were studied in some patients. The microspheres were found to cause problems with inflammation (Chiang, et al., Clinical Pharmacology and Therapeutics, 1984, 36, 704). A major problem with the microspheres is that the naltrexone cannot be removed from the body once it has been injected. Thus, should a patient require narcotics for medical reasons such as in the case of a serious accident or broken bone, he or she would be unable to derive any benefit from narcotic-type painkillers as long as the microspheres were still active in the body. Also, the inability to remove naltrexone microspheres is a problem if there is an allergic response to naltrexone, which is known to occur.

Microspheres have been used in small trials to treat alcoholics. Injection into the gluteus maximus produced blood levels above 1 ng/ml for about 20 days. The overall release was not zero-order. Rather, it declined steadily over about 40 days (Kranzler, et al., Alcoholism: Clinical and Experimental Research, 1998, 22, 1074).

Drug Abuse Sciences recently announced the beginning of clinical trials involving a microsphere injectable dosage form (NALTREL®) that would deliver naltrexone over a 30-day period (http://www.drugabusesciences.com/products.asp). The problems inherent in this system have been mentioned above. Additionally, naltrexone is depleted at a

rate that varies among patients. This variability among patients could create a significant problem with drug buildup and risk of toxicity because subsequent injections need to be given to ensure complete blockage in all patients, especially those whose blood levels of naltrexone decrease the fastest. Patients who have slower metabolism, however, will still have large amounts of naltrexone in their bloodstream, and subsequent injections may possibly push them into an overdose situation.

3. Biodegradable implant - A long-acting implant has been designed and patented by Sidman (U.S. Patent No. 4,351,337). This implant incorporates the drug into a poly-alpha-amino acid structure. The structure is biodegradable and slowly dissolves in the body. The drug may be incorporated into a matrix of the poly-alpha-amino acid and then slowly released by hydrolysis, or it may be contained within a closed structure of the poly-alpha-amino acid and then diffuse out. Alternatively, the drug may be released through a combination of both hydrolysis and diffusion. The patent specifically mentions that narcotic antagonists, including naltrexone, may be used with such a delivery system. Examples 3,4 and 5 disclose that naltrexone could be used with such a system but they do not disclose or suggest that the release can be done in a zero order.

In U.S. Patent No. 4,450,150, Sidman employs an implantable poly (glutamic acid-ethyl glutamate) structure. Specifically, in example 1 he describes a rod-shaped implant containing 21.1mg of naltrexone. He was able to demonstrate a near zero order release rate for 24 days and extrapolated that the drug release may last longer since only one third of the naltrexone had been released within the twenty-four days. There are significant shortcomings with this invention, however. First, the implant has only been shown to be effective for 24 days. Second, the implant is by nature an erodible device. When it incorporates the drug into the poly (glutamic acid-ethyl glutamate) structure, the release cannot be zero order because the surface area of the implant gets smaller and smaller over time. While this structure has demonstrated a 24 day release, the structure is not suitable for long-term, zero order release. Alternatively, the drug may be enclosed within the poly (glutamic acid-ethyl glutamate) structure. At some point, the structure must erode and then the release rate cannot be zero order. Third, the fact that the implant is designed not to be removed means that subsequent implants can create a toxicity problem. At the end of the delivery cycle there will always be a fall off in the release rate. At some point, the release rate falls below the therapeutic value or the minimum effective concentration (MEC). At this point, if patients require more

naltrexone, it could be dangerous to insert another implant because the dosage released by the new implant and the residual dosage from the old one have an additive effect that could push concentrations in the bloodstream to a toxic level.

4. Transdermal delivery system - A transdermal delivery system has been developed by Glier, et al. (U.S. Patent No. 4,806,341) which promises to deliver doses of narcotic antagonists such as naloxone (Narcan) through the skin. This system, however, would not address any of the effectiveness criteria identified above since patients could easily remove it. It therefore would not represent a significant improvement over the oral administration of naltrexone in terms of effectiveness and patient compliance.

Thus, based upon the prior disclosure, there exists a need for a system and method for delivering a therapeutic agent over a extended period of time in conjunction with an initial loading dose of the therapeutic agent. While the background art has been examined particularly in the area of narcotic antagonists, this examination is in no means considered to be limiting but rather serves to illustrate the need for the system and method of the present invention.

Summary of the Invention

The system and method of the present invention address the above-described shortcomings in prior art delivery systems for delivering therapeutic agents requiring an initial loading dose administered in conjunction with a long-term maintenance delivery of the therapeutic agent. In particular, the system and method of the present invention are useful for the administration of naltrexone and other narcotic antagonists in the treatment of opioid addiction, alcoholism and other addictions.

One object of this invention is to provide a system whereby a single administration of a therapeutic agent will provide sufficient plasma levels of the agent in patients to treat the disease/disorder for at least six months. Thus, the drug delivery system of this invention must be sufficiently efficient to provide effective levels of a therapeutic agent for at least six months with a dose of the drug that can be practically incorporated into a non-erodible, subcutaneous-implantable dosage form. This duration of release is critical because the usual poor compliance of patients, particularly for products used to treat addiction, often results in relapse within the first 6 to 12 months. A preferred system of the present invention exists whenever the implantable dosage form is in the form of a hydrogel tube. The preferred

hydrogel tube can be modified so that the system releases the therapeutic agent more quickly or slowly depending upon the disease/disorder to be treated.

A further, object of the present invention utilizes the non-erodible, subcutaneous-implantable dosage form of a therapeutic agent of the present invention in conjunction with a loading dose of the therapeutic agent. The loading dose may take the form of any dosing method known to one of skill in the art such as, for example, oral, parenteral, intravenous and subcutaneous implant.

Another objective of this invention is to provide the optimal dose and rates of delivery of a therapeutic agent such as, for example, naltrexone and other narcotic antagonists that will produce the minimum effective concentration (MEC) of the antagonist in a particular patient's bloodstream for the required duration of time. A system according to this invention must define at least two treatment phases, each of which has its own minimum serum concentration value and therefore its own delivery rates for any implantable device. The defined optimal release rate profile for a particular agent such as, for example, the narcotic antagonist naltrexone, can be derived through a method that combines different types of dosage forms including oral, subcutaneous and intramuscular injections, and subcutaneous inserts of non-erodible delivery devices such as hydrogel implants, silastic tubes or osmotic pump implants that are capable of providing multiple release rates.

Brief Description of the Drawings

Figure 1 - illustrates the *in vitro* release rates of naltrexone from various hydrogel, subcutaneous-implantable dosage forms having different percent values of Equilibrium Water Content (%EWC).

Detailed Description of the Invention

The present invention describes a system and method for administering a loading dose of a therapeutic agent concurrently with a subcutaneous-implantable dosage form, which releases the therapeutic agent over an extended period of time, to a patient in need of such a therapeutic regimen. Diseases/disorders which may be beneficially treated by the system and method of the present invention include the following: addictive disorders such as, for example, narcotic addiction, alcohol addiction and craving and nicotine addition; psychiatric disorders; infectious diseases such as, for example, post-operative infections;

cardiovascular diseases; respiratory diseases such as, for example, tuberculosis; inflammatory conditions such as, for example, rheumatoid arthritis; immune-based diseases such as, for example, hypersensitivity; auto-immune diseases such as, for example, multiple sclerosis; bone diseases; and tumor causing and non-tumor causing cancers.

The subcutaneous-implantable dosage forms of the present invention can take the form of any such dosage form known in the art such as, for example, non-erodible implants. Subcutaneous-implantable dosage forms provide many advantages for long-term drug administration for the following reasons:

1. They administer the drug to the patient in a defined manner precluding the need for active participation by the patient in the administration of the drug;

2. They administer the drug in a dose and dose rate to produce drug levels higher than the minimum effective concentration (MEC) throughout the duration of treatment;

3. They administer the drug in a dose and dose rate to produce drug levels close to the MEC to minimize any chances of toxicity and to maximize the efficiency and cost of the system;

4. They minimize the first pass exposure to the liver, decreasing the potential for hepatoxicity; and

5. They decrease intestinal and hepatic first pass metabolism increasing systemic availability.

Specifically, non-erodible subcutaneous-implantable dosage forms provide many advantages over erodible forms for the following reasons:

1. They can be removed by trained medical personnel in the event of an emergency in which other therapeutic agents must be administered, which are not compatible with the drug being administered by the subcutaneous dosage form;

2. They can be removed when the delivery rate falls below the MEC so that subsequent implants can be inserted without any risk of unnecessary drug buildup and toxicity; and

3. They can be removed if an allergic reaction to the drug occurs.

Additionally, the subcutaneous-implantable dosage forms may take the form of hydrogels, silastic tubes and osmotic devices. Preferred dosage forms of the present invention are non-erodible hydrogels. Small cylindrical implants with thin walls that can predictably control the rate of drug release can be constructed using the class of compounds

referred to as hydrogels. These compounds are biocompatible; they resist biodegradation and do not support microbial growth. They consist of various esters of methacrylic acid such as, for example, hydroxyethyl methacrylate and hydroxypropyl methacrylate that are copolymerized to form a polymer matrix that incorporates water. The water-filled pores of the matrix allow drug molecules to diffuse from the interior to the surrounding bulk fluid. When the bulk fluid is the interstitial fluid surrounding the cells in the body, the drug released is expected to be absorbed into the blood circulation, thence to be delivered to the sites of action in the body where the drug will exert its pharmacologic effects.

It is possible to adjust the Equilibrium Water Content (EWC) to obtain specified release rates. The following illustration of the invention was developed using the procedures described by Kuzma (Kuzma, et al., "Long-term drug delivery from subcutaneous hydrogel implants", Proceedings, Controlled Release Society Conference on Protein/Peptide Controlled-Release Delivery. Baltimore MD Aug. 21-22, 1996 and Kuzma, et al., US Patent 5,266,325). Homogeneous Polymers of 2-hydroxymethyl acrylate (HEMA), methacrylic acid, and 1,1,1, Trimethylol propane trimethyl acrylate (TMPTMA) were prepared, as described by Kuzma, such that the relative concentrations are in the range needed to produce certain values of the equilibrium water content (EWC). These EWC values result in *in vitro* rates in the range expected to produce the desired concentration-time profile.

The initial loading dose of therapeutic agent in the system and method of the present invention may take the form of any method of drug administration known to one of skill in the art such as, for example, oral, parenteral, intravenous or subcutaneous implant. The preferred method of administration will vary upon the disease/disorder to be treated and the therapeutic agent chosen for the treatment regimen.

The method of the present invention determines the desired dose of therapeutic agent needed to achieve the desired plasma levels of the therapeutic agent as well as the corresponding rates of delivery required to effectively treat the disease/disorder for the six to twelve month life of the subcutaneous-implantable dosage form. There are at least two phases of drug administration in the method of the present invention: the Receptor Loading Dose (RLD); and Maintenance Phase (MP). Optionally, the method of the present invention may include a third phase known as the Initial Loading Dose (ILD) at the initiation of dosing. Further discussion outlining the process to determine the optimal drug delivery rates for each of these phases will be presented for the narcotic antagonist, naltrexone.

Phase I (ILD) - Days one to two. Immediately after implants are administered, there may be a lag time of 1 or 2 days for the drug to diffuse through the rate-controlling membrane and surrounding tissues before it reaches the bloodstream. During this time period, a rapidly available source of the drug can be administered as an initial loading dose to quickly produce effective levels until the drug from the implants reaches effective levels. This initial loading dose can be given orally for one or two days. Alternatively, one of the implants could be coated with a rapidly dissolving drug coat.

Phase II (RLD) - Days two to thirty. During this period, the dosage of drug is lower than that in Phase I but higher than that in Phase III. The higher serum levels of this phase serve two purposes. First, for the particular therapeutic agent chosen, the long-term maintenance dose releases drug slowly at a constant (zero order) rate. This produces the most efficient, longest acting means of delivering the drug. It has the disadvantage, however, that the plasma level will slowly rise until it reaches a plateau, which is referred to as steady state. The time to reach steady state is a function of the drug's half-life, a measure of the time it takes for half of the drug to be eliminated from the body. It takes approximately six half-lives to reach steady state for any drug. As will be shown below the narcotic antagonist, naltrexone has an effective half-life of almost 100 hours. So it will take about 20 days before steady state is reached for naltrexone. During this time it is essential that an additional source of drug be administered as a receptor loading dose to continue to saturate the drug receptors. A second reason for this loading dose, particularly for drugs used to treat addictions, is to prevent cravings and other withdrawal symptoms.

Phase III (MP) - Months one to Twelve. During this period, the MEC is lower and the system of the present invention can be tailored to maintain plasma concentration above the MEC at steady state in an efficient zero order manner.

The method for optimizing drug delivery during each of these phases are based upon an analysis of the pharmacokinetic and pharmacodynamic properties of the therapeutic agent administered and clinical observations. The following discussion includes first, a description of the method of delivering the optimal drug delivery rate to allow a practical dose of drug, administered one time, to maintain adequate plasma levels from six to twelve months. This is followed by a description of how the drug delivery system can be further optimized, based upon a pharmacokinetic model of the interaction of the drug with its receptor binding sites in the body and clinical observations.

After adequate blood levels have been achieved during Phase I and Phase II, the ideal delivery system should provide a prolonged constant blood level above the MEC. An objective of the invention is to provide a drug delivery system that will deliver the drug at an optimal rate and optimal levels to ensure that the therapeutic agent will have the desired therapeutic effects for the maximum duration of time. It is generally agreed that the ideal delivery system would provide a zero order input, that is, a constant rate, in the MP. This MP (Phase III) should provide a zero order input sufficient to maintain steady state plasma levels above the MEC of the selected therapeutic agent. This parsimonious, "drug-sparing" input will allow a single administration of the dosage form to provide effective maintenance levels for the longest period possible. Ideally, it would be advantageous to have a system that would release drug for a year or more. At least a six month period is possible based upon an interpretation of the pharmacokinetic data available in the literature for naltrexone, a preferred embodiment of this invention.

The following discussion illustrates the steps necessary to determine an MEC for a therapeutic agent, according to the present invention. Additionally, the following discussion illustrates how one of skill in the art may use the calculated MEC data to formulate a dosage form that will release the therapeutic agent over an extended period of time to a patient in need of such therapeutic agent. The following discussion, while specifically related to narcotic antagonists and more specifically the narcotic antagonist, naltrexone, is not intended to limit and shall not be construed to limit the system and method of the present invention but rather serves to illustrate the novelty and utility of the system and method of the present invention. It is expected that one of ordinary skill in the art would be able to apply the system and method described herein to a wide variety of therapeutic agents.

Determination of the Dosage Rate for Phase III (MP)

A reinterpretation of the pharmacokinetic data available in the literature, which is disclosed below, utilizing the concepts of the present invention, demonstrate that a therapeutic agent can be delivered in a substantially zero order manner for a period between about six months and about twelve months with the system and method of the present invention.

The zero order rate of delivery (D/T) of the dose (D), delivered constantly over a given period of time (T), that is required to reach a desired steady state, minimum effective

plasma concentration (MEC), for a given plasma clearance (CL), is given by the well-known equation:

$$(D/T) = CL \times MEC$$

The prior art states that the plasma half life of naltrexone, a well-known narcotic antagonist, is about 2 to about 10 hours and the corresponding plasma clearance is about 2 to about 4 L/min (Chiang, et al., Clinical Pharmacology and Therapeutics, 1984, 36, 704 and Willette, et al., eds., "Narcotic Antagonists: Naltrexone Pharmacochemistry and Sustained-Release Preparation", NIDA Research Monograph 28, 1981). Therefore, the maintenance dosage rate necessary to achieve a MEC of 2 ng/ml may be calculated using the equation:

$$D/T = (3\ L/min \times 60\ min/hr \times 24\ hr/day)(2\ mcg/L) = 8.64\ mg/day$$

Such a dosage rate would require a dose of 1.56 g in a zero order controlled release implantable dosage form to provide effective levels for six months. This required dose is greater than possible with current implantable dosage form technologies. A reinterpretation of several prior art studies utilizing the teaching of the present invention demonstrates that the dosage rate at steady state is considerably less, thereby allowing a given dose to provide effective levels for a greater period of time.

Important new information was provided by Lee (Lee, et al., J. Nucl. Med. 1998, 29, 1207). Using new positron emission tomography (PET) technology with ^{11}C-carbfentenil, they recently disclosed that when the μ-opiate receptors in the brain are occupied by naltrexone (thus blocking the effects of opioids), the dissociation of naltrexone from the receptor followed a monoexponential decline corresponding to a half-life of approximately 72 hours, which corresponds to a first-order rate constant of 0.0096/hr. The time course of occupancy of naltrexone on the opioid receptors in the human brain was found to be much longer than would have been predicted by most previous blood level studies. The percent blockade of opiate receptors by 50 mg of oral naltrexone was 90 to 100% for 48 hours, followed by the monoexponential decline. Lee points out that this is similar to the long half-life of 96 hours observed by Verebey and coworkers (Verebey, et al., Clinical Pharmacology and Therapeutics 1976, 315) in the third exponential phase of the naltrexone plasma-concentration time curve (at 24 to 72 hours following a 100 mg dose of naltrexone).

It is noteworthy that Verebey, et al., did not associate the long terminal elimination phase with the opioid receptors. They disregarded the terminal half-life in their

assessment of the dosage rate (D/T) required to produce an effective plasma level in the maintenance phase. In a subsequent paper, they estimated D/T to be 11.8 g/kg/hr (Kogan, et al., Res. Com. Chem. Path. and Pharmacol., 1977, 18, 29). This corresponds to a daily dose of 20.4 mg/day for a 72 kg person, or a total dose of 3.67 grams for six months. Again this is not possible with currently available drug delivery systems.

A reinterpretation of these data, utilizing the disclosure of the present invention is based on the following assumptions:

1. The terminal plasma concentration observed by Verebey, et al., represents distribution equilibrium between the brain opioid receptors and the systemic plasma compartment, which occurs in the terminal exponential phase after a single dose, and at steady state after continuous (zero order) dosing;

2. Therefore, the terminal half-life ($t_{1/2}(3)$) in the plasma represent the half-life of naltrexone dissociating from the receptors. This concept provides an alternative way, using only plasma concentration-time data, to obtain the receptor dissociation half-life for other narcotic antagonists that is much simpler and less costly than the ^{11}C PET method used by Lee, et al. In fact it can be used for any drug in which the dissociation from the receptor is the slowest distribution step;

3. As the brain receptors and systemic plasma are in distribution equilibrium at the time that the terminal exponential phase occurs, the volume of distribution of the receptor compartment is the same as the volume of distribution for the terminal phase (V_3);

4. The clearance term representing loss of naltrexone from the brain receptors is determined using the following equation,

$$Cl_3 = V_3 \times k_3$$

where V_3 and k_3 are calculated from the plasma concentration time curve; and

5. When steady state distribution equilibrium occurs, the rate of dosing to the receptors will be equal to the rate of loss of antagonist from the receptors. The Maintenance Dosage Rate (D/T) is calculated by the following equation,

$$D/T = MEC \times V_3 \times k_3$$

The teachings of the present invention show that the estimates of plasma clearance and therefore the maintenance dose needed to reach a given MEC are actually much lower than the rates taught by the prior art. Further, the teachings of the present invention

demonstrate that the time needed to reach steady state equilibrium using a zero order maintenance does is longer than the times taught in the prior art.

The present invention teaches that to achieve at least 98% blocking of the opioid receptors, with the inherent variability between patients, a Maintenance Dose Rate of from about 250 to about 1500 microgram/day is necessary.

Phase II Concentration Requirements

Additionally, the teachings of the present invention take into account the fact that steady state does not occur immediately but requires a period of time to reach distribution equilibrium. A period of approximately 3.3 half-lives is necessary to achieve a 90% receptor occupancy level. For naltrexone, if the maintenance rate is set to reach the plasma level corresponding to a 90% occupancy level at distribution equilibrium, the time to reach this level is calculated as 3.3 x 72 hr, which is about equal to about 10 days. To reach a 98% occupancy with naltrexone will require about 20 days. This period of time necessary to reach distribution equilibrium is the reason that the Receptor Loading Dose of the present invention is necessary to provide a new and useful system and method for delivering therapeutic agents.

Variable Rate Requirements

To provide sufficient blocking levels over the entire period required for the maintenance dose to reach steady state, two or three types of inserts could inserted simultaneously. One would produce a higher initial rate for a short period of time (e.g., 2 weeks to 2 months). This would serve as the receptor loading dose to ensure that plasma and brain levels would be significantly above the 100% receptor occupancy level during the time (10 to 20 days) that it takes for the implants with the slower maintenance rate to reach steady state distribution levels in the plasma and the brain.

There are additional advantages in maintaining higher levels during the first 1 to 2 months. During this period, the addict is most likely to test the blocking power of the implant, perhaps using larger than usual narcotic doses. It is critical during this conditioning period that the patient is prevented from overcoming the blockade of the receptor. Moreover, if the opioid receptors are not completely blocked during the initial treatment phase (Phase I and II), some patients receiving naltrexone may use heroin to reduce craving. The following clinical study in one such subject illustrates this problem.

Example 1

K.R. - is 41 year old white male who has had a problem with heroin addiction for about six years. A URD was performed (ultra rapid detox or anesthesia assisted opiate detoxification) and a pellet of naltrexone was inserted simultaneously which contains 1g of naltrexone and 12.5mg of triampcinalone. In other patients, this pellet has been found to completely block the euphoric effects of self administration of heroin or any other narcotics, even in large doses. However, the patient had some persistent withdrawal symptoms following his detoxification and used some heroin. He reported that this made him feel more comfortable with his withdrawal symptoms although he did not experience a euphoria. He continued to do this on a regular basis and said that the heroin would reliably decrease his withdrawal symptoms, particularly low energy, decreased appetite, and insomnia. An investigation was conducted to compare the effectiveness of the naltrexone pellet with the higher blood levels of naltrexone that can be achieved with oral administration.

With only the naltrexone pellet in place providing a low naltrexone blood level, an intravenous (IV) administration was conducted over a 30 minute period comprising a series of six injections, three of which were normal saline and three of which were morphine sulfate for a total dose of 50 mg. Clinical evaluation indicated mild relief of withdrawal symptoms but no euphoria. Administration of a 1mg of naloxone (Narcan) was given to reverse the effects of the total of 50 mg morphine resulting in a return to a baseline level of withdrawal symptoms. Then in Phase II of the experiment, the patient received 100mg of oral naltrexone. Approximately five hours later, when the Naltrexone blood level was higher, the same experiment was repeated. In this second phase, four injections, two with Morphine sulfate (l25mg) and two with normal saline were administered. This time there was no subjective or objective change in any withdrawal symptoms and no euphoria. When we reversed the Morphine with naloxone (Narcan 2mg) there was no change in his withdrawal symptoms. With the second experiment, a higher dose of naltrexone was delivered by the oral medicine as a supplement to the pellet. In this case, there was no override of the blockage effects and no inducement of withdrawal symptom relief or euphoria, even with a dose of 50 mg of Morphine sulfate.

In this study, a higher amount of naltrexone was necessary to overcome the craving even though a euphoric high was blocked by a lower dose of naltrexone. There are several possible mechanisms that might explain these results. One is that craving may be

related in part to other sites of action that require higher levels of naltrexone to block them. An alternative explanation is that the craving still occurs at a higher level of occupancy of the opiate receptors than the "high" effect. The data of Verebey, et al., suggest that the opiate high rating was blocked longer after a single dose than the "liking" rating which in turn correlated with the amount the subjects were willing to spend for a heroin dose (Verebey, et al., Clinical Pharmacology and Therapeutics 1976, 315). These results suggest that higher levels of naltrexone are needed for the latter effects, regardless of the mechanism. Since the extinguishment of conditioned responses is so critical during the early phase of treatment, a multi-phase drug delivery system is necessary (O'Brien, et al., "Naltrexone in a Behavioral Treatment Program", NIDA Research Monograph 1976, 136; O'Brien, et al., J. Clin. Psychiatry, 1984, 45, 53; and Tai, et al., NIDA Treatment Workshop "Nalterxone - An Antagonist Therapy for Heroin Addiction", November 12-13, 1997). Phase II (months 1 to 2) provides higher levels than the minimum needed to prevent narcotic highs. This ensures that attempts to use high doses to override the naltrexone blockage will be thwarted. The higher levels may be necessary in some patients to overcome craving symptoms that occur early during treatment while the extinguishment of conditioned response is being initiated in the behavioral component of the treatment program. For pharmacokinetic reasons, the higher levels are also needed until the steady state distribution levels are reached through the slower maintenance dose. A subcutaneous product that delivers drug at a zero order rate of 0.56mg/day will produce a steady state level of about 7.5 ng/ml, which is greater than the concentration required, when equilibrated with brain levels, to produce complete receptor occupancy after about 10 to 30 days.

Phase I Concentration Requirements

To reach effective blood levels immediately, a "loading dose" of 50 to 100 mg may be given orally for one to three days or it may be incorporated into the subcutaneously administered dosage form. The amount of loading dose would be given by the formula:

LOADING DOSE =VOLUME OF DISTRIBUTION X MEC

This amount could be coated on the outside of the cylindrical insert for immediate release to provide drug for the first few days.

The above calculations for naltrexone are based upon values from the literature on clearance values and the MEC, as well studies which relate brain occupancy to observed clinical responses. The combination of extensive accumulated data and our conceptual approaches to provide optimal input rates for naltrexone represents an advance in the state of the art for providing long lasting therapeutic effects. This general method of optimizing delivery to maximize the time during which a given dose provides an effective amount of drug is applicable to any narcotic antagonist, including but not limited to naltrexone, nalmefene, and cyclozine. The antagonist is administered subcutaneously in an erodible or non-erodible implantable insert in which the rate of delivery can be controlled and predicted by *in vitro* release rates, such as hydrogels, silastic tubes or osmotic devices. A preferred embodiment of this new method of optimizing naltrexone administration follows.

Cylindrical polymer tubes, as above described, were produced from the hydrogel compounds and filled with ±5 mg of anhydrous naltrexone base (Mallinkrodt) and stearic acid, NF. The tube was sealed at both ends to form an implant approximately 35 mm in length. The *in vitro* release of hydrogels of varying EWC (37.7%; 40.4%; 46.0%; 60.6%; 65.8%) was measured by placing the Hydrogels in elution vials containing approximately 10 ml of elution medium at 37°C and analyzed by a validated HPLC assay. Three implants of each composition were tested. The mean release rates were obtained weekly. The mean rates plotted as a function of time are shown in Figure 1. The final delivery system involves the subcutaneous implantation of one or more implants for the loading dose (Phase II) and implantation of one or more implants for long term maintenance (Phase III). One of these implants may be coated with an immediate initiating dose (Phase I). Alternatively, the initiating dose can be given orally, e.g., 50 to 100 mg naltrexone tablets for days 1-2.

An example of ranges of values that would constitute this invention is shown in the table below:

PERIOD	PERIOD 1	PERIOD 2	PERIOD 3
FUNCTION	initiating dose	receptor loading/ relapse prevention	maintenance dose
DURATION	1-2 DAYS	2-60 DAYS	180 to 360 DAYS
TARGET BLOOD LEVELS	20-60 ng/ml	4-10 ng/ml	1-4 ng/ml

DOSE	50-100 mg Oral 5-10 mg parenteral	65 mg (1 tube)	65 mg (1 tube) to 230 mg (4 tubes)
RATE	Immediate (bolus)	500-2000 μg/day	250-1500 μg/day

The final composition of the implants is determined by experimentally measuring the plasma concentrations that result from the tested implants in volunteers. Morphine challenges can be done in selected volunteers/patients to validate clinical effectiveness and determine the rang of naltrexone concentration values that serve as the MEC.

These data are used to optimize the final dosage form. This system allows the overall dosage regimen to be individualized by varying the number and rate of the individual dosage forms. In this way, treatment can be tailored to the needs of the individual patient.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of this invention and, without departing from its spirit or scope, can make various changes and modifications in the invention to adapt it to various usages and conditions, such changes and modifications are hereby covered by the present invention.

Claims:

1. A system for administering a therapeutic agent to a patient in need of the agent, comprising:

at least one receptor loading dosage form containing the therapeutic agent; and

at least one extended-release dosage form containing the therapeutic agent, wherein the receptor loading dosage form and the extended-release dosage form are administered substantially concurrently.

2. The system according to claim 1, wherein the at least one receptor loading dosage form is selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

3. The system according to claim 1, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

4. The system according to claim 3, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

5. The system according to claim 4, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

6. The system according to claim 5, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

7. The system according to claim 1, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders, psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases,

inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

8. The system according to claim 7, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addiction.

9. The system according to claim 8, wherein the disorder is narcotic addiction.

10. The system according to claim 9, wherein the therapeutic agent is a narcotic antagonist.

11. The system according to claim 10, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

12. The system according to claim 11, wherein the narcotic antagonist is naltrexone.

13. A system for administering a therapeutic agent to a patient in need of the agent, comprising:

at least one initial loading dosage form containing the therapeutic agent;

at least one receptor loading dosage form containing the therapeutic agent; and

at least one extended-release dosage form containing the therapeutic agent,

wherein the at least one initial loading dosage form, the at least one receptor loading dosage form and the at least one extended-release dosage form are administered substantially concurrently.

14. The system according to claim 13, wherein the at least one initial loading dosage form and the at least one receptor loading dosage form are independently selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

15. The system according to claim 14, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

16. The system according to claim 15, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

17. The system according to claim 16, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

18. The system according to claim 17, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

19. The system according to claim 13, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders, psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases, inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

20. The system according to claim 19, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addition.

21. The system according to claim 20, wherein the disorder is narcotic addiction.

22. The system according to claim 21, wherein the therapeutic agent is a narcotic antagonist.

23. The system according to claim 22, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

24. The system according to claim 23, wherein the narcotic antagonist is naltrexone.

25. A method of treating a patient in need of a therapeutic regimen, comprising the following steps:

administering at least one receptor loading dosage form containing the therapeutic agent; and

administering at least one extended-release dosage form containing the therapeutic agent, wherein the at least one receptor loading dosage form and the at least one extended-release dosage are administered substantially concurrently.

26. The method according to claim 25, wherein the at least one receptor loading dosage form is selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

27. The method according to claim 26, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

28. The method according to claim 27, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

29. The method according to claim 28, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

30. The method according to claim 29, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

31. The method according to claim 25, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders,

psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases, inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

32. The method according to claim 31, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addition.

33. The method according to claim 32, wherein the disorder is narcotic addiction.

34. The method according to claim 33, wherein the therapeutic agent is a narcotic antagonist.

35. The method according to claim 34, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

36. The method according to claim 35, wherein the narcotic antagonist is naltrexone.

37. A method of treating a patient in need of a therapeutic regimen, comprising the following steps:

administering at least one initial loading dosage form containing the therapeutic agent;

administering at least one receptor loading dosage form containing the therapeutic agent; and

administering at least one extended-release dosage form containing the therapeutic agent, wherein said initial loading dosage form, receptor loading dosage form and extended-release dosage form are administered substantially concurrently.

38. The method according to claim 37, wherein the at least one initial loading dosage form and the at least one receptor loading dosage form are independently selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or

subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

39. The method according to claim 38, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

40. The method according to claim 39, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

41. The method according to claim 40, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

42. The method according to claim 41, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

43. The method according to claim 37, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders, psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases, inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

44. The method according to claim 43, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addition.

45. The method according to claim 44, wherein the disorder is narcotic addiction.

46. The method according to claim 45, wherein the therapeutic agent is a narcotic antagonist.

47. The method according to claim 46, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

48. The method according to claim 47, wherein the narcotic antagonist is naltrexone.

49. A method of delivering a therapeutic agent to a patient in need of the therapeutic agent, comprising the following steps:

determining an optimal dose and an optimal rate of delivery of the therapeutic agent sufficient to produce a minimum effective concentration of the therapeutic agent in the patient's bloodstream for a period of at least six months;

administering at least one receptor loading dosage form containing the therapeutic agent, wherein the at least one receptor loading dosage form releases the therapeutic agent at such a rate as to effectively load the patient's drug receptors until a steady state minimum effective concentration is achieved from at least one extended-release dosage form containing the therapeutic agent; and

administering the at least one extended-released dosage form containing the therapeutic agent, wherein the at least one receptor loading dosage form and the at least one extended-release dosage form are administered substantially concurrently.

50. The method according to claim 49, wherein the optimal rate of administration is calculated to be approximately equal to the rate at which the therapeutic agent leaves the receptors in the patient's body, at a steady state.

51. The method according to claim 50, wherein the at least one extended-release dosage form is adapted and configured to release the therapeutic agent in a substantially zero order manner.

52. The method according to claim 51, wherein the at least one extended-release dosage form is adapted and configured to release the therapeutic agent for about six to about twelve months.

53. The method according to claim 52, wherein the at least one receptor loading dosage form is selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

54. The method according to claim 53, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

55. The method according to claim 54, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

56. The method according to claim 55, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

57. The method according to claim 56, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

58. The method according to claim 49, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders, psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases, inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

59. The method according to claim 58, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addition.

60. The method according to claim 59, wherein the disorder is narcotic addiction.

61. The method according to claim 60, wherein the therapeutic agent is a narcotic antagonist.

62. The method according to claim 61, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

63. The method according to claim 62, wherein the narcotic antagonist is naltrexone.

64. A method of delivering a therapeutic agent to a patient in need of the therapeutic agent, comprising the following steps:

determining an optimal dose and an optimal rate of delivery of the therapeutic agent sufficient to produce a minimum effective concentration of the therapeutic agent in the patient's bloodstream for a period of at least six months;

administering at least one initial loading dosage form containing the therapeutic agent;

administering at least one receptor loading dosage form containing the therapeutic agent, wherein the at least one receptor loading dosage form releases the therapeutic agent at such a rate as to effectively load the patient's drug receptors until a steady state minimum effective concentration is achieved from at least one extended-release dosage form containing the therapeutic agent; and

administering the at least one extended-released dosage form containing the therapeutic agent, wherein the at least one initial loading dosage form, the at least one receptor loading dosage form and the at least one extended-release dosage form are administered substantially concurrently.

65. The method according to claim 64, wherein the optimal rate of administration is calculated to be approximately equal to the rate at which the therapeutic agent leaves the receptors in the patient's body, at a steady state.

66. The method according to claim 65, wherein the at least one extended-release dosage form is adapted and configured to release the therapeutic agent in a substantially zero order manner.

67. The method according to claim 66, wherein the at least one extended-release dosage form is adapted and configured to release the therapeutic agent for about six to about twelve months.

68. The method according to claim 67, wherein the at least one initial loading dosage form and the at least one receptor loading dosage form are independently selected from the group consisting of oral dosage forms, parenteral dosage forms (intramuscular or subcutaneous), intravenous dosage forms, a coating on the at least one extended-release dosage form and implantable dosage forms.

69. The method according to claim 68, wherein the at least one extended-release form is a non-erodible, implanted, subcutaneous dosage forms.

70. The method according to claim 69, wherein the non-erodible, implanted, subcutaneous dosage form is selected from the group consisting of hydrogels, silastic tubes and osmotic pumps.

71. The method according to claim 70, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form.

72. The method according to claim 71, wherein the at least one extended release dosage form is a non-erodible, implanted, subcutaneous, hydrogel dosage form fashioned from a co-polymer of various esters of methacrylic acid.

73. The method according to claim 64, wherein the therapeutic agent is useful for treating diseases and disorders selected from the group consisting of addictive disorders, psychiatric disorders, infectious diseases, cardiovascular diseases, respiratory diseases, inflammatory conditions, immune-based diseases, auto-immune diseases, bone diseases and cancers.

74. The method according to claim 73, wherein the disorder is selected from the group consisting of narcotic addiction, alcohol addiction and craving and nicotine addition.

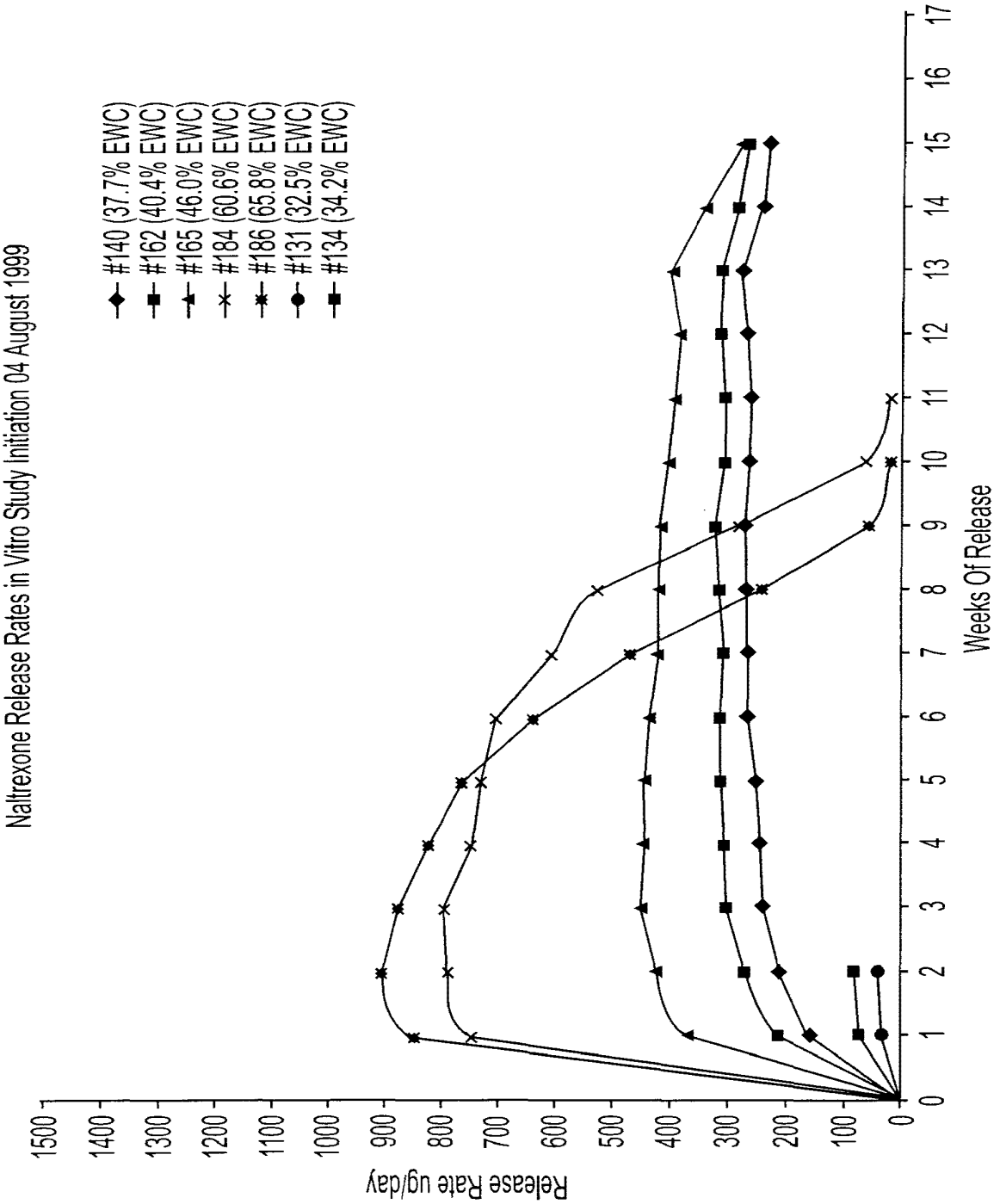
75. The method according to claim 74, wherein the disorder is narcotic addiction.

76. The method according to claim 75, wherein the therapeutic agent is a narcotic antagonist.

77. The method according to claim 76, wherein the narcotic antagonist is selected from the group consisting of naltrexone, naloxone, cyclazocine and nalmefene.

78. The method according to claim 77, wherein the narcotic antagonist is naltrexone.

Fig. 1


Naltrexone Release Rates in Vitro Study Initiation 04 August 1999
#140 (37.7% EWC)
#162 (40.4% EWC)
#165 (46.0% EWC)
#184 (60.6% EWC)
#186 (65.8% EWC)
#131 (32.5% EWC)
#134 (34.2% EWC)
Release Rate ug/day
Weeks Of Release
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
0
1
2
3
4
5
6
7
8
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34386

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/24
US CL :424/473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/473

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

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

DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,760,044 A (ARCHER) 02 June 1998, column 3, line 55 to column 4 and line 63, column 11, lines 37-68 and column 12, lines 24-49.	1-78
Y	US 5,965,567 A (ARCHER et al) 12 October 1999, column 3, lines 20-58, column 7, lines 30-66, column 8, lines 48-52, column 10, lines 6-35, example 2 and claims 16-22.	1-78
A	US 5,985,880 A (CHANG et al) 16 November 1999.	1-78
A	US 5,512,587 A (SPECTOR) 30 April 1996.	1-78
A	US 5,846,974 A (KALLMAN et al) 08 December 1998.	1-78

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
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"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		

Date of the actual completion of the international search 06 FEBRUARY 2001	Date of mailing of the international search report 21 MAR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BLESSING FUBARA Telephone No. (703) 308-0196

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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	
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	6495155	B1	2002-12-17	Tice, et al.	

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					

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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	01/43726	WO	A	2001-06-21	Trident Tech LLC		☐

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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	
	Attorney Docket Number	4000.3010 US1

	1	Reuning, R.H., et al., "Pharmacokinetic quantitation of naltrexone release from several sustained-released delivery," NIDA. Research Monograph, Institute on Drug Abuse, 28:172-184, (1981).	☐
	2	Yolles, S., et al., "Long acting delivery for narcotic antagonists II: release reates of naltrexone from Poly(lactic acid) composites," PDA J. of Pharm. Sci and Tech., 64(2):348-349, (1995)	☐

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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	
	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)	2008-07-16
Name/Print	Darlene A. Vanstone	Registration Number	35,729

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.**

Electronic Acknowledgement Receipt

EFS ID:	3630790
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:	17-JUL-2008
Filing Date:	17-MAR-2005
Time Stamp:	10:09:48
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	Information Disclosure Statement Letter	4thSIDS.pdf	66784 b67ecdce11de4cfd92cd77f9c249665b63e7619b	no	3

Warnings:	
Information:	

2	Foreign Reference	ESR.pdf	2480591 4d8905fd0b5776efede79a9adc996880de57acfb	no	5
Warnings:					
Information:					
3	NPL Documents	REUNING.pdf	8714221 a24b67b04308aa73c8d270fc44a05235c72a4196	no	14
Warnings:					
Information:					
4	NPL Documents	YOLLES.pdf	2240414 09a9b9f931c6decae30688e9564c267625cb76b2	no	2
Warnings:					
Information:					
5	Foreign Reference	WO0143726.pdf	1535043 8780e712c735eee75f7003fc6d91fd0c40afcb06	no	32
Warnings:					
Information:					
6		4th1449.pdf	32320 a8cf21745bf0cdc6fa3b49f778603b973f15daf5	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Information Disclosure Statement (IDS) Filed	1	2
Information Disclosure Statement Letter	3	3

Warnings:	
Information:	
Total Files Size (in bytes):	15069373

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 Art Unit: 1617

Filed: March 17, 2005 Examiner: Not Yet Assigned

Confirmation No.: 8002

Title: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

3rd 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)

[X] 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).

[ ] under 37 CFR 1.97(c) together with either:
- [ ] 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)

[ ] 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)

[ ] 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:

[**X**] Copies of the cited references are enclosed.

[ ] 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.

[ ] Please charge Deposit Account [ ] in the amount of [$].

[X] Please charge any deficiency in fees and credit any overpayment to Deposit Account 502807.

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: **July 9, 2008**

PTO/SB/08a (03-08)
Approved for use through 06/30/2008. OMB 0651-0031
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 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	
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					

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] i	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							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

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	
	Attorney Docket Number	4000.3010 US1

	1	HEINALA, Pekka et al., "Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial," J Clinical Psychopharmacology, 21(3):287-292 (2001).	☐
	2	"Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)," Addiction Treatment Forum, Ed., LEAVITT, Stewart, pp. 1-8 (2002).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	Application Number	11083167
	Filing Date	2005-03-17
	First Named Inventor	Elliot Ehrich
	Art Unit	1617
	Examiner Name	
	Attorney Docket Number	4000.3010 US1

CERTIFICATION STATEMENT

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☒ 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)	2008-07-09
Name/Print	Darlene A. Vanstone	Registration Number	35,729

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	3589627
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:	09-JUL-2008
Filing Date:	17-MAR-2005
Time Stamp:	16:12:23
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	NPL Documents	Heinala.pdf	92762 077ec6ec2536527fa09312202b2843a521209189	no	6

Warnings:	
Information:	

2	NPL Documents	Naltrexone.pdf	153061 9043c7d7121ca16f9f43e93e409da4578da7daaa	no	8
Warnings:					
Information:					
3	Information Disclosure Statement Letter	3rdSIDS.pdf	66883 9e374413747f86210a7c8155dd06f38cbad8ca04	no	3
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed	3rd1449.pdf	31384 0252ea2721eb7a6be1c7cb7fcf8fb7b218811e51	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	344090	

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
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New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/08a (03-08)
Approved for use through 06/30/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	
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					

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] i	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							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

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	
	Attorney Docket Number	4000.3010 US1

	1	O'MALLEY, Stephanie S. et al., "Initial and Maintenance Naltrexone Treatment for Alcohol Dependence Using Primary Care vs Specialty Care. A Nested Sequence of 3 Randomized Trials," ARCH INTERN MED., 163: 1695-1704 (2003).	☐
	2	LATT, Noeline C. et al., "Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting," MJA, 176: 530-534 (2002).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	Application Number	11083167
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☒ 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)	2008-06-19
Name/Print	Darlene A. Vanstone	Registration Number	35,729

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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: Not Yet Assigned

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)

[**X**] 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).

[ ] under 37 CFR 1.97(c) together with either:
- [ ] 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)

[ ] 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:

[**X**] Copies of the cited references are enclosed.

[ ] 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.]

[**X**] The listed references were cited 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 [ ] in the amount of [$]. A copy of this Statement is enclosed.
[X] Please charge any deficiency in fees and credit any overpayment to Deposit Account 502807.

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

Westford, MA 01886
Dated: June 19, 2008

Electronic Acknowledgement Receipt

EFS ID:	3499200
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/Rachel Meehan
Filer Authorized By:	Darlene Vanstone
Attorney Docket Number:	4000.3010 US1
Receipt Date:	23-JUN-2008
Filing Date:	17-MAR-2005
Time Stamp:	12:32:53
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	Information Disclosure Statement (IDS) Filed	SuppIDS.pdf	28678 e2d9eb7eabc6ee376d1265a267225df31cc1af3b	no	3

Warnings:	
Information:	

This is not an USPTO supplied IDS fillable form					
2	Information Disclosure Statement Letter	SuppIDSLtr.pdf	59788 16d2be89871aa44273f269de4e5a448bf2279fd0	no	3
Warnings:					
Information:					
3	NPL Documents	Ref1OMalley.pdf	129315 fbbfc0f28b07d601bb4fc70df96a0540fb959adc	no	10
Warnings:					
Information:					
4	NPL Documents	Ref2Latt.pdf	141288 54a4174c3115fc18af0cfaec4f9b4a49b2bcbf11	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	359069	

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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.

Docket No: 4000.3010 US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich

Application No: 11/083,167 Group No: 1617

Filed: March 17, 2005 Examiner: Carter, Kendra D.

Confirmation No.: 8002

Title: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

CERTIFICATE OF TRANSMISSION I hereby certify that this correspondence is being electronically filed at the United States Patent and Trademark Office on: /Hollie Wakefield/ September 5, 2007
Signature Date **HOLLIE WAKEFIELD**
Typed or printed name of person signing certificate

PRELIMINARY AMENDMENT

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

Sir:

Please amend the application as follows:

Amendments to the Specification begin on page **2.**

Amendments to the Claims are reflected in the listing of claims which begins on page **5** of this paper.

Amendments to the Claims:

Please cancel Claims 24 and 25.

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

Claim Listing:

1. (Original) 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. (Original) A method of treating an individual in need of naltrexone comprising administering a 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. (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. (Original) The method of Claim 3 wherein the naltrexone is administered in a long acting formulation comprising naltrexone.

5. (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. (Original) A method of treating an individual in need of naltrexone comprising administering a 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 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. (Original) 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. (Original) 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. (Original) 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. (Original) 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. (Canceled)

25. (Canceled)

Remarks/Arguments

Claims 24 and 25 have been cancelled. Claims 1-23 are pending in the application. Reconsideration is respectfully requested.

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.

/Carolyn S. Elmore/

By_____

Carolyn S. Elmore
Registration No.: 37,567
Tel.: (978) 251-3509
Fax: (978) 251-3973

N. Chelmsford, MA 01863
Dated: **September 5, 2007**

Electronic Acknowledgement Receipt

EFS ID:	2161633
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:	Carolyn S. Elmore/Hollie Wakefield
Filer Authorized By:	Carolyn S. Elmore
Attorney Docket Number:	4000.3010 US1
Receipt Date:	05-SEP-2007
Filing Date:	17-MAR-2005
Time Stamp:	17:40:43
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	Preliminary Amendment	PLA.pdf	89507 796c6cd65f578286fe1f98d80663139648c16fc7	no	5
Warnings:					

Information:	
Total Files Size (in bytes):	89507

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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
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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 09/05/2007	(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 $50=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $200=	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:
Jacquelyn L. Williams

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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Elmore, Craig & Vanstone
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FACSIMILE COVER SHEET

Date: December 1, 2005

To: Group 1614

From: Carolyn S. Elmore, Esq.
Registration No. 37,567

Fax Number: **(571) 273-8300**

Subject:

Paper:	Supplemental Information Disclosure Statement with Form PTO-1449
Docket No.:	4000.3010 US1
Applicant:	Elliot Ehrich
Serial No.:	11/083,167
Filing Date:	March 17, 2005

Number of pages including this cover sheet 16

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Elmore, Craig & Vanstone, P.C., 209 Main Street, Chelmsford, MA 01863, USA. voice: (978) 251-3509 / fax (978) 251-3973 . www.elmorecraig.com

PAGE 1/16 * RCVD AT 12/1/2005 3:21:46 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/28 * DNIS:2738300 * CSID: * DURATION (mm-ss):06-06

Docket No: 4000.3010 US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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DEC 0 1 2005

Applicant: Elliot Ehrich

Application No.: 11/083,167 Group Art Unit: 1614

Filed: March 17, 2005 Examiner: Not Yet Assigned

Confirmation No.: 8002

Title: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

CERTIFICATE OF MAILING OR TRANSMISSION
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12-1-05 Hollie Wakefield

Date Signature

HOLLIE WAKEFIELD

Typed or printed name of person signing certificate

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)

[X] 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).

[ ] under 37 CFR 1.97(c) together with either:
- [ ] 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)

[ ] 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)

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[X] Enclosed herewith is form PTO-1449:

[X] A copy of the cited reference (DA) is enclosed.

[ ] 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.

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[ ] 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.

11/083,167

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 [ ] in the amount of [$]. A copy of this Statement is enclosed.
[X] Please charge any deficiency in fees and credit any overpayment to Deposit Account 502807.

Respectfully submitted,

ELMORE, CRAIG & VANSTONE, P.C.

By
Carolyn S. Elmore
Registration No.: 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

N. Chelmsford, MA 01863
Dated: 12/1/05

PTO-1449 REPRODUCED	ATTORNEY DOCKET NO.	APPLICATION NO.	
INFORMATION DISCLOSURE CITATION IN AN APPLICATION	4000.3010 US1	11/083,167	
December 1, 2005	APPLICANT: Elliot Ehrich		
(Use several sheets if necessary)	FILING DATE: March 17, 2005	CONFIRMATION NO.: 8002	GROUP: 1614

		OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*
	DA	Bartus, *et al.*, Vivitrex®, an Injectable, Extended-Release Formulation of Naltrexone, Provides Pharmacokinetic and Pharmacodynamic Evidence of Efficacy for 1 Month in Rats," *Neuropsychopharmacology*, 28:1973-1982 (August 2003).

EXAMINER	DATE CONSIDERED

OIPE JC56
AUG 29 2005
PATENT & TRADEMARK OFFICE

Docket No: 4000.3010 US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich

Application No.: 11/083,167 Group Art Unit: 1614

Filed: March 17, 2005 Examiner: Not Yet Assigned

Confirmation No.: 8002

Title: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

CERTIFICATE OF MAILING OR TRANSMISSION
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8/25/05 Rachel Meehan
Date Signature

RACHEL MEEHAN
Typed or printed name of person signing certificate

INFORMATION DISCLOSURE STATEMENT

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

Sir:

This Information Disclosure Statement is submitted:

[ ] under 37 CFR 1.129(a), or
(First/Second submission after Final Rejection)

[X] 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).

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- [ ] a Statement under 37 CFR 1.97(e), as checked below, or
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Statement Under 37 CFR 1.97(e)

[ ] 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.

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[ ] 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:

[X] Copies of the cited references (BA-BD, AL-AM & AR-AR2) 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:

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Respectfully submitted,

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	BA	60/554,658	03-19-2004	Elliott Ehrich, *et al.*
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		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.		

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(54) Title: POLYMORPHIC FORMS OF NALTREXONE

(57) Abstract: This invention relates to the discovery of novel polymorphic forms of naltrexone, including solvates, hydrates, anhydrous and other crystalline forms and combinations thereof. These novel forms of naltrexone impart advantages in pharmaceutical formulations incorporating them, including sustained release, or long acting, formulations.

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POLYMORPHIC FORMS OF NALTREXONE

BACKGROUND OF THE INVENTION

Alcohol dependence is a prevalent disease with substantial morbidity and mortality. Detoxification and psychosocial therapy provide the basis of treatment; in addition, pharmacotherapy is becoming widely accepted. Administered orally, naltrexone, a potent opioid antagonist, has been shown to reduce relapse to heavy drinking in alcohol dependent patients, decrease the number of drinks consumed when relapse does occur, and promote abstinence. Naltrexone has been reported to reduce both craving and the reinforcing euphoric qualities of alcohol.

Although naltrexone has been shown to be effective as a maintenance agent in the treatment of alcohol dependence, a major limitation of its utility can be poor adherence to therapy. In the treatment of alcohol abuse, oral naltrexone must be taken on a daily basis. In a clinical trial comparing oral naltrexone to placebo, greater than 40% of patients treated with naltrexone were noncompliant with the daily oral regimen. In medication-noncompliant patients relapse to clinically significant drinking was similar to placebo treated patients and significantly higher than the rate observed with medication-compliant patients.

Polymorphs, solvates and salts of various drugs have been described in the literature as imparting novel properties upon the drug. These polymorphs can have different solubilities, stabilities and processing characteristics, presenting opportunities and challenges.

SUMMARY OF THE INVENTION

This invention relates to the discovery of novel amorphous and polymorphic forms of naltrexone, including solvates, solvatomorphs, hydrates, anhydrous and other crystalline forms and combinations thereof. These novel forms of naltrexone impart advantages in pharmaceutical formulations incorporating them, including sustained release, or long acting, formulations. The solvates, or solvatomorphs, can include stoichiometric and non-stoichiometric solvates, such as clathrates, for example.

The present invention provides polymorphic forms of naltrexone which are characterized by X-ray Powder Diffraction (XRPD), differential scanning calorimetry (DSC) or attenuated total reflectance infrared absorption spectroscopy (IR-ATR).

The present invention advantageously provides novel polymorphic forms of naltrexone comprising naltrexone ethanolate, anhydrous naltrexone, naltrexone monohydrate, benzyl alcohol solvate and other polymorphs of naltrexone either isolated or in combination.

In another aspect, the invention, provides methods of making novel polymorphic forms of naltrexone comprising (i) mixing a naltrexone, such as a naltrexone base anhydrous and/or hydrochloride or other salt, with a solvent selected from the group consisting of acetonitrile, dimethyl formamide, water, methanol, ethanol, benzyl alcohol, dichloromethane, acetone, ethyl acetate, methyl ethyl ketone, toluene and hexane; (ii) heating the mixture to within 1-10°C of the boiling point to prepare a nearly saturated solution; (iii) cooling the resulting nearly saturated solution to room temperature forming precipitated material; and (iv) harvesting the precipitated material.

A further aspect of the invention provides pharmaceutical compositions containing the naltrexone forms disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated, but in no way limited, by the Tables herein and the following examples, with reference to the figures in which:

Figure 1A is a graph depicting the X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling from acetonitrile (dipolar aprotic).

Figure 1B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using acetonitrile (dipolar aprotic).

Figure 2A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using dimethyl formamide (dipolar aprotic).

Figure 2B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using dimethyl formamide (dipolar aprotic).

Figure 3 is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using water (protic).

Figure 4A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using methanol (protic).

Figure 4B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using methanol (protic).

Figure 5A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using ethanol (protic).

Figure 5B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using ethanol (protic).

Figure 6 is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using benzyl alcohol (protic).

Figure 7A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using dichloromethane (Lewis acidic).

Figure 7B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using dichloromethane (Lewis acidic).

Figure 8A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using acetone (Lewis basic).

Figure 8B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using acetone (Lewis basic).

Figure 9A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using ethyl acetate (Lewis basic).

Figure 9B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using ethyl acetate (Lewis basic).

Figure 10A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using methyl ethyl ketone (Lewis basic).

Figure 10B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using methyl ethyl ketone (Lewis basic).

Figure 11A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using toluene (aromatic).

Figure 11B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using toluene (aromatic).

Figure 12A is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by slow cooling using hexane (non-polar).

Figure 12B is a graph depicting X-ray Powder Diffraction (XRPD) patterns of crystalline naltrexone formed by fast cooling using hexane (non-polar).

Figure 13A is a graph depicting a DSC of crystalline naltrexone formed by slow cooling using acetonitrile (dipolar aprotic).

Figure 13B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using acetonitrile (dipolar aprotic).

Figure 14A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using dimethyl formamide (dipolar aprotic).

Figure 14B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using dimethyl formamide (dipolar aprotic).

Figure 15 is a graph depicting DSC of crystalline naltrexone formed by fast cooling using water (protic).

Figure 16A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using methanol (protic).

Figure 16B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using methanol (protic).

Figure 17A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using ethanol (protic).

Figure 17B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using ethanol (protic).

Figure 18 is a graph depicting DSC of crystalline naltrexone formed by fast cooling using benzyl alcohol (protic).

Figure 19A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using dichloromethane (Lewis acidic).

Figure 19B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using dichloromethane (Lewis acidic).

Figure 20A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using acetone (Lewis basic).

Figure 20B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using acetone (Lewis basic).

Figure 21A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using ethyl acetate (Lewis basic).

Figure 21B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using ethyl acetate (Lewis basic).

Figure 22A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using methyl ethyl ketone (Lewis basic).

Figure 22B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using methyl ethyl ketone (Lewis basic).

Figure 23A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using toluene (aromatic).

Figure 23B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using toluene (aromatic).

Figure 24A is a graph depicting DSC of crystalline naltrexone formed by slow cooling using hexane (non-polar).

Figure 24B is a graph depicting DSC of crystalline naltrexone formed by fast cooling using hexane (non-polar).

Figure 25A is a graph depicting IR-ATR of crystalline naltrexone formed by slow cooling using acetonitrile (dipolar aprotic).

Figure 25B is a graph depicting IR-ATR of crystalline naltrexone formed by fast cooling using acetonitrile (dipolar aprotic).

Figure 26A is a graph depicting IR-ATR of crystalline naltrexone formed by slow cooling using dimethyl formamide (dipolar aprotic).

Figure 26B is a graph depicting IR-ATR of crystalline naltrexone formed by fast cooling using dimethyl formamide (dipolar aprotic).

Figure 27 is a graph depicting IR-ATR of crystalline naltrexone formed by fast cooling using water (protic).

Figure 28A is an IR-ATR of crystalline naltrexone formed by slow cooling using methanol (protic).

Figure 28B is an IR-ATR of crystalline naltrexone formed by fast cooling using methanol (protic).

Figure 29A is an IR-ATR of crystalline naltrexone formed by slow cooling using ethanol (protic).

Figure 29B is an IR-ATR of crystalline naltrexone formed by fast cooling using ethanol (protic).

Figure 30 is an IR-ATR of crystalline naltrexone formed by fast cooling using benzyl alcohol (protic).

Figure 31A is an IR-ATR of crystalline naltrexone formed by slow cooling using dichloromethane (Lewis acidic).

Figure 31B is an IR-ATR of crystalline naltrexone formed by fast cooling using dichloromethane (Lewis acidic).

Figure 32A is an IR-ATR of crystalline naltrexone formed by slow cooling using acetone (Lewis basic).

Figure 32B is an IR-ATR of crystalline naltrexone formed by fast cooling using acetone (Lewis basic).

Figure 33A is an IR-ATR of crystalline naltrexone formed by slow cooling using ethyl acetate (Lewis basic).

Figure 33B is an IR-ATR of crystalline naltrexone formed by fast cooling using ethyl acetate (Lewis basic).

Figure 34A is an IR-ATR of crystalline naltrexone formed by slow cooling using methyl ethyl ketone (Lewis basic).

Figure 34B is an IR-ATR of crystalline naltrexone formed by fast cooling using methyl ethyl ketone (Lewis basic).

Figure 35A is an IR-ATR of crystalline naltrexone formed by slow cooling using toluene (aromatic).

Figure 35B is an IR-ATR of crystalline naltrexone formed by fast cooling using toluene (aromatic).

Figure 36A is an IR-ATR of crystalline naltrexone formed by slow cooling using hexane (non-polar).

Figure 36B is an IR-ATR of crystalline naltrexone formed by fast cooling using hexane (non-polar).

Figure 37 is the DSC of an ethanolate (clathrate) form of naltrexone.

Figure 38 is a graph showing a 2-Theta scale crystallinity of a naltrexone-containing microparticle composition of the instant invention as a function of process steps.

Figure 39 is an XRPD in 2-Theta scale of a representative composition of the instant invention.

Figure 40 is a bar graph representing the mean polymorph distribution as reported in Table 5A.

Figure 41A is a graph representing the effect of the percentage of crystallinity of a composition of the instant invention on its *in vitro* drug release.

Figure 41B is a graph representing the effect of the percentage of crystallinity of a composition of the instant invention on its *in vivo* drug release.

Figure 42 is a DSC of amorphous naltrexone.

Figure 43 is an XRPD pattern for naltrexone base anhydrous.

Figure 44 is an XRPD pattern for naltrexone monohydrate.

Figure 45 is an XRPD pattern for naltrexone benzyl alcohol solvate

Figure 46 is an XRPD pattern for naltrexone ethanolate.

Figure 47 is a graph illustrating the effect of crystallinity on microparticle impurity generation at controlled room temperature.

Figure 48 is a graph illustrating the effect of crystallinity on microparticle decay at controlled room temperature.

Figure 49A and 49B illustrate the effect of crystallinity on *in vitro* and *in vivo* drug release.

DETAILED DESCRIPTION OF THE INVENTION

In the course of research, Applicants surprisingly discovered novel naltrexone polymorphs, including solvates, hydrates and anhydrous forms and combinations thereof. Further investigation led to the realization that favorable

properties in naltrexone-containing microparticles were due to the crystalline forms and non-crystalline forms of the naltrexone contained within the microparticles. Applicants appreciated that the polymorphic forms of naltrexone crystalline, for example, the ethanol solvate form of naltrexone, have good to superior properties in naltrexone-containing compositions.

Pharmaceutical compositions when formulated for administration are useful in the treatment and prevention of, for example, narcotic or alcohol addiction and autism, as well as other naltrexone-based therapies.

As with all pharmaceutical compounds and compositions, the chemical and physical properties of the naltrexone form(s) utilized can be important in its commercial development. These properties include, but are not limited to: (1) packing properties such as molar volume, density and hygroscopicity, (2) thermodynamic properties such as melting temperature, vapor pressure and solubility, (3) kinetic properties such as dissolution rate and stability (including stability at ambient conditions, especially to moisture, and under storage conditions), (4) surface properties such as surface area, wettability, interfacial tension and shape, (5) mechanical properties such as hardness, tensile strength, compactibility, handling, flow and blend; and (6) filtration properties. These properties can affect, for example, processing and storage of pharmaceutical compositions comprising naltrexone. Solid state forms of naltrexone that provide an improvement in one or more of these properties relative to other solid state forms of naltrexone are desirable.

The polymorphs of the invention and the compositions containing them have the advantage that they are in a form which provides for improved ease of handling. Further, depending upon the intended use, they have improved chemical and solid state stability. For example, they may be stable when stored over prolonged periods of time. They may be prepared in good yields, in higher purity, in less time, more conveniently and at a lower cost, than forms of naltrexone prepared previously.

1. Crystallization of naltrexone in a variety of solvents

A series of naltrexone samples were generated by the crystallization of bulk drug substance at different rates out of a variety of solvents. These materials have

been characterized by x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and attenuated total reflectance infrared absorption spectroscopy (IR-ATR).

The isolated crystal form of a substance often is a function of the nature of the crystallization solvent and of the rate it is crystallized out of that solvent. The solvents in the following list include representatives from all solvent classes, and crystallization out of these enable unique crystal forms accessible to naltrexone.

Table 1.

Solvent System Type	Preferred Solvents
Dipolar aprotic	Acetonitrile, Dimethyl formamide
Protic	Water, Methanol, Ethanol, Benzyl alcohol
Lewis acidic	Dichloromethane
Lewis basic	Acetone, Ethyl acetate, Methyl ethyl ketone
Aromatic	Toluene
Non-polar	Hexane

2. Methods for Identifying the Novel Forms

Applicants prepared substantially pure polymorphic forms of naltrexone using two separate processes. In one process, Applicant prepared the crystalline naltrexone polymorphs using a slow cooling process ("slow"). Commercially available naltrexone base anhydrous (Mallinckrodt) was dissolved in solvent forming a solvent system. The resulting solvent system was heated to within 1-10°C of the boiling point for purpose of preparing a nearly saturated solution. The nearly saturated solution was then cooled to room temperature at a rate not greater than 1-2°C/min. The resulting precipitated material was harvested.

The second process was a fast cooling process ("fast") wherein naltrexone base anhydrous (Mallinckrodt) was dissolved in solvent forming a solvent system. The resulting solvent system was heated to within 5-10°C of the boiling point for purpose of preparing a nearly saturated solution. The nearly saturated solution was

then cooled as rapidly as possible to room temperature. The resulting precipitated material was harvested.

Table 2 below is a summary of each solvent used, which process was employed, and a reference to the Figure which shows the results of each of the three analytical methods performed.

3. X-ray Powder Diffraction

Most of the various crystalline forms of naltrexone were analyzed using X-ray Powder Diffraction. X-ray powder diffraction (XRPD) patterns were obtained using a Rigaku MiniFlex powder diffraction system, equipped with a horizontal goniometer in the θ /2-θ mode. The x-ray source was nickel-filtered K-α emission of copper (1.54056 Å). Samples were packed into an aluminum holder using a back-fill procedure, and were scanned over the range of 50 to 6 degrees 2-θ, at a scan rate of 0.5 degrees 2-θ/min. Calibration of each powder pattern was effected using the characteristic scattering peaks of aluminum at 44.738 and 38.472 degrees 2-θ and these peaks are seen in the pattern. Other XRPDs were analyzed using a Bruker D8 Advance XRD or a SCINTAC X-ray diffractometer (model #XDS 2000), using 0.02°/step with a 1 second interval. Samples were scanned over the range of 2 to 40 degrees 2-θ at a scan rate of 1 degree 2-θ/min.

XRPD powder patterns of the various naltrexone precipitated materials obtained by the slow and fast cooling from a variety of solvent systems are shown herein in the Figures. The naltrexone forms of the invention are not limited to those made in accordance with the methods described herein.

4. Melting/Decomposition Temperature

The temperatures of melting and/or decomposition of naltrexone crystalline forms were determined using differential scanning calorimetry (DSC). Most DSC measurements, were obtained on a TA Instruments 2910 thermal analysis system. Samples of approximately 1-2 mg were accurately weighed into an aluminum DSC pan, and covered with an aluminum lid that was crimped in place. The samples were then heated over the range of 25-240°C, at a heating rate of 10°C/min.

Table 2.

	Slow Cooling Process			Fast Cooling Process		
Solvent	XRPD	DSC	IR-ATR	XRPD	DSC	IR-ATR
Acetonitrile	Fig. 1a	Fig. 13a	Fig. 25a	Fig. 1b	Fig. 13b	Fig. 25b
Dimethyl formamide	Fig. 2a	Fig. 14a	Fig. 26a	Fig. 2b	Fig. 14b	Fig. 26b
Water	/////	/////	/////	Fig. 3	Fig. 15	Fig. 27
Methanol	Fig. 4a	Fig. 16a	Fig. 28a	Fig. 4b	Fig. 16b	Fig. 28b
Ethanol	Fig. 5a	Fig. 17a	Fig. 29a	Fig. 5b	Fig. 17b	Fig. 29b
Benzyl alcohol	/////	/////	/////	Fig. 6	Fig. 18	Fig. 30
Dichloromethane	Fig. 7a	Fig. 19a	Fig. 31a	Fig. 7b	Fig. 19b	Fig. 31b
Acetone	Fig. 8a	Fig. 20a	Fig. 32a	Fig. 8b	Fig. 20b	Fig. 32b
Ethyl acetate	Fig. 9a	Fig. 21a	Fig. 33a	Fig. 9b	Fig. 21b	Fig. 33b
Methyl ethyl ketone	Fig. 10a	Fig. 22a	Fig. 34a	Fig. 10b	Fig. 22b	Fig. 34b
Toluene	Fig. 11a	Fig. 23a	Fig. 35a	Fig. 11b	Fig. 23b	Fig. 35b
Hexane	Fig. 12a	Fig. 24a	Fig. 36a	Fig. 12b	Fig. 24b	Fig. 36b

//// = not available

Melting/decomposition temperature ranges were defined from the extrapolated onset to the maximum of the melting/decomposition endotherm.

Other DSC measurements were obtained by TA Instruments Q 1000 DSC using hermetic pans and a DSC ramp method using a heating rate of 10°C/min. or 50°C/min. from 0°C to 200°C. Those skilled in the art will recognize other appropriate means of measuring DSC.

DSC thermograms of the various naltrexone materials obtained by slow and fast cooling from a variety of solvent systems are shown in the Figures.

5. Infrared Absorption Spectroscopy

The solid-state infrared (IR) spectrum of the analyte was obtained using a Buck Scientific model M-500 infrared spectrometer, operating in the single beam mode, and using the attenuated total reflectance (ATR) detection mode. The sample was clamped against the ZnSe crystal single reflection horizontal ATR sampling accessory, sold under the tradename MIRacle™ by Pike Technologies.

IR-ATR spectra of the various Naltrexone products obtained by slow and fast cooling from a variety of solvent systems are shown in the Figures.

Naltrexone Ethanolate

In particular, the Applicants prepared a polymorphic form of naltrexone ethanolate which is characterized by an X-ray powder diffraction with a characterizing peak at about 9° (2θ). This peak appears irrespective of which of the two processes for preparing were employed.

The resulting analysis showed that the polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figure 5A. The polymorphic form can be further characterized by the DSC pattern of Figure 17A and/or the IR-ATR of Figure 29A.

This polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figure 5B. The polymorphic form can be further characterized by the DSC pattern of Figure 17B and/or the IR-ATR of Figure 29B.

A polymorphic form of naltrexone ethanolate can also be characterized by Figure 46. A purified naltrexone ethanolate according to the invention can be

prepared in the substantial absence of one or more polymorphic forms of naltrexone selected from the group consisting of, for example, naltrexone benzyl alcohol solvate, naltrexone monohydrate, and anhydrous naltrexone. As used herein, the "substantial absence" is intended to mean having no or negligible (including detectable) amounts of the identified substance, as can be arrived at by processes intending to avoid the formation of the identified substance or by processes intended to remove the identified substance.

Further, a polymorphic form according to the invention can be prepared wherein the form is in the complete absence of naltrexone benzyl alcohol solvate, as can be arrived at by employing a process which avoids the use of benzyl alcohol as or in the solvent system. In another embodiment, the polymorphic form is present with naltrexone benzyl alcohol solvate, and in amount of at least about 88% or less than about 65% by weight of total crystalline naltrexone or, alternatively, is not present in an amount of about 67.0%, 76.3 or 85.7% by weight of total crystalline naltrexone.

An ethanolate form of naltrexone characterized by the XRPD in Figures 5A, 5B or 46 are examples of a form in the absence of naltrexone benzyl alcohol solvate.

Of particular interest to those skilled in the art is a polymorphic form of the invention wherein the form is substantially pure.

Anhydrous Form

Other forms of the invention are contemplated. For example, an anhydrous polymorphic form of naltrexone was prepared which form can be characterized by an X-ray powder diffraction with a characterizing peak at about 8° (2θ).

For example, the polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figure 1A. Additionally, this polymorphic form can be further characterized by the DSC pattern of Figure 13A. Still further, this polymorphic form can be characterized by the IR-ATR of Figure 25A.

Such a polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figure 1B. Still further, the polymorphic form can be further characterized by the DSC pattern of Figure 13B. Additionally, this polymorphic form can be further characterized by the IR-ATR of Figure 25B.

Alternatively or additionally, the polymorphic form can be characterized by the XRPD of Figure 43.

Monohydrate

Applicants also prepared a monohydrate form of naltrexone formed by using water as the solvent. This polymorphic form of naltrexone is characterized by an X-ray powder diffraction with a characterizing peak at about 7° (2θ). This polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figures 3 and 44. Further, the polymorphic form at about 7 can be characterized by the DSC pattern of Figure 15. Additionally, the polymorphic form can be further characterized by the IR-ATR of Figure 27.

Benzyl Alcohol Solvate

Applicants have prepared another polymorphic form of naltrexone which can be characterized by an X-ray powder diffraction with a characterizing peak at about 5-6° (2θ). Additionally, a polymorphic form of naltrexone can be characterized by the X-ray powder diffraction pattern of Figures 6 and 45. Still further, the polymorphic form can be characterized by the DSC pattern of Figure 18. Also, a polymorphic form can be characterized by the IR-ATR of Figure 30.

Further, a polymorphic form according to the invention can be prepared wherein the form is in the complete absence of naltrexone ethanolate, as can be arrived at by employing a process which avoids the use of ethanol as or in the solvent system. In another embodiment, the polymorphic form is present with naltrexone ethanolate, and in amount of at least about 35% or less than about 13% by weight of total crystalline naltrexone or, alternatively, is not present in an amount of about 33.0%, 23.7 or 14.3% by weight of total crystalline naltrexone.

Other polymorphs, including the solvates specifically described herein and combinations thereof, are a part of the invention.

Amorphous Naltrexone

Applicants have also prepared an amorphous form of naltrexone which can be characterized by the DSC pattern of Figure 42. Amorphous naltrexone form was

prepared by leaving NTX base in 180-190°C oven for approximately 10 minutes. After being melted, it was taken out to cool at room temperature. It was then broken up into small pieces using a spatula and ground into fine powders using mortar and pestle. The X-ray powder diffraction pattern confirmed that the powder was amorphous.

Methods of making an isolated and/or substantially pure form or mixture of forms of naltrexone

The forms can be prepared by a method comprising: (i) mixing a naltrexone, such as a naltrexone base anhydrous or a salt, such as hydrochloride, with a solvent or solvent system containing one or more organic or aqueous solvents, such as acetonitrile, dimethyl formamide, water, methanol, ethanol, benzyl alcohol, dichloromethane, acetone, ethyl acetate, methyl ethyl ketone, toluene and hexane; (ii) heating the solvent or solvent system to within about 1-10°C of the boiling point to prepare nearly saturated solutions; (iii) slowly cooling the resulting nearly saturated solutions to room temperature, such as at a rate not greater than 1-2°C/min, thereby forming precipitated materials; and (iv) harvesting the precipitated materials. This method is also referred to herein as the slow process or cooling method.

Examples of materials prepared by this method can be characterized by the X-ray powder diffraction pattern selected from the group consisting of Figures 1A, 2A, 4A, 5A, 7A, 8A, 9A, 10A, 11A, and 12A.

Still further, precipitated materials prepared by this method can be characterized by the DSC pattern selected from the group consisting of Figures 13A, 14A, 16A, 17A, 19A, 20A, 21A, 22A, 23A and 24A. Additionally, the precipitated materials can be characterized by the IR-ATR selected from the group consisting of Figures 25A, 26A, 28A, 29A, 31A, 32A, 33A, 34A, 35A, and 36A.

Alternatively, Applicants prepared the polymorphs of the instant invention by the method comprising: (i) mixing a naltrexone base anhydrous with a solvent selected from the group consisting of acetonitrile, dimethyl formamide, water, methanol, ethanol, benzyl alcohol, dichloromethane, acetone, ethyl acetate, methyl ethyl ketone, toluene and hexane; (ii) heating the solvent or solvent system to within

about 5-10°C of the boiling point to prepare nearly saturated solutions; (iii) quickly cooling the resulting nearly saturated solutions, such as rapidly as possible, to about room temperature, or less, thereby forming precipitated materials; and (iv) harvesting the precipitated materials. This is also referred to herein as the fast process or cooling method.

Material prepared by the fast method can be characterized by the X-ray powder diffraction pattern selected from the group consisting of Figures 1B, 2B, 3, 4B, 5B, 6, 7B, 8B, 9B , 10B, 11B, and 12B. Further, precipitated materials prepared by this method can be characterized by the DSC pattern selected from the group consisting of Figures 13B, 14B, 15, 16B, 17B, 18, 19B, 20B, 21B, 22B, 23B and 24B. Additionally, they can be characterized by the IR-ATR selected from the group consisting of Figures 25B, 26B, 27, 28B, 29B, 30, 31B, 32B, 33B, 34B, 35B, and 36B.

In one embodiment, the novel forms can be manufactured during the process for producing the formulation, such as the specific process for formulating the extended release formulation, referred to herein as formulation A, as described below in the exemplification. In yet another embodiment, the invention excludes the extended release formulation, formulation A, described below in the exemplification.

Mixtures of Polymorphic Forms

Applicants have discovered that compositions comprising mixtures of two or more forms and/or mixtures of crystalline and non-crystalline drug possess particular advantages in extended release formulations. Thus, the invention also relates to mixtures of such naltrexone products.

In one aspect of the invention, the naltrexone comprises a mixture of crystalline and non-crystalline forms. For example, the % crystallinity of the naltrexone can be at least about 10%, preferably at least about 20% (by weight) of the total naltrexone, preferably in an amount of at least about 30%, at least about 40%, at least about 50%, at least about 60% (by weight) of the total naltrexone. In one embodiment the % crystallinity of naltrexone is present in an amount between about 10% and 70%, preferably between about 30% and 50% (by weight), of the

total naltrexone. In another embodiment, the % crystallinity is not 41%, 34.3%, or 35.2% of total naltrexone.

The crystalline naltrexone present in such compositions can be any crystalline form of naltrexone. Preferably the crystalline form includes naltrexone ethanolate, more preferably naltrexone ethanolate clathrate. The naltrexone ethanolate is preferably present in the crystalline form in an amount of at least about 40% by weight, more preferably in an amount of at least about 50% by weight, more preferably in an amount of about 60% by weight.

Non-crystalline naltrexone can be in the form of amorphous and/or dissolved naltrexone relative to the composition or composition matrix. By amorphous (or free amorphous) naltrexone is meant that the amorphous form exists as a separate phase, such as when present in the matrix. By dissolved naltrexone is meant drug and matrix exist as a single phase. An example of a dissolved naltrexone includes a naltrexone present in a polymeric extended release formulation wherein the naltrexone is dissolved in polymeric matrix. Such an extended release device includes that described in the exemplification below.

Thus, in one aspect of the invention, the non-crystalline naltrexone in the naltrexone composition can be from 0-100% by weight dissolved, preferably at least about 20% is dissolved, more preferably at least about 50% is dissolved, more preferably at least about 80% is dissolved. In one embodiment, substantially all of the non-crystalline form is dissolved naltrexone.

The inventions also include mixtures of the forms described herein. Thus, the inventions include, for example, naltrexone ethanolate (such as, naltrexone ethanolate clathrate) alone or in combination with one or more of the other forms described herein (in the presence, absence or substantial absence of non-crystalline (amorphous and/or dissolved) naltrexone). Such combinations can include compositions that have between 0 and 100% by weight of any particular form. The composition preferably includes naltrexone ethanolate. Preferred amounts of naltrexone ethanolate include at least about 10% by weight of total crystalline product, preferably at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% by weight of total crystallinity. In one preferred embodiment, the

naltrexone ethanolate is present in the amount of about 60%. In another embodiment, the naltrexone ethanolate is absent in the amount of about 60%. The percentages represent the fraction of crystallinity as determined by relative peak intensity of characterizing peaks.

In yet another aspect, compositions of the invention are prepared wherein the crystalline naltrexone is in the substantial absence of a polymorphic form of naltrexone selected from the group consisting of: naltrexone benzyl alcohol solvate, naltrexone monohydrate, and anhydrous naltrexone. Such compositions preferably possess naltrexone ethanolate, such as naltrexone ethanolate clathrate, in the preferred amounts described above.

A preferred mixture includes about 50-70% naltrexone ethanolate and the balance naltrexone benzyl alcohol solvate. Another mixture includes about 10-15% of naltrexone monohydrate; about 10-15% naltrexone anhydrous; about 10-15% naltrexone benzyl alcohol solvate; and the balance of the composition is naltrexone ethanolate. Of course, the claimed invention may include other mixtures of naltrexone forms as well, including mixtures characterized by two or three of the above forms, substituting one or more other forms for one or more of the above, (including, but not limited to, one or more of the other forms described herein), modifying the amounts of one or more of the forms, adding an additional form, etc.

Utility

The present invention provides a method for the treatment of a patient afflicted with addictive diseases or central nervous system disorders wherein such disease states may be treated by the administration of an effective amount of naltrexone of the present invention to a patient in need thereof.

Thus, where the composition is being administered to treat addictive behavior, a therapeutically effective amount of naltrexone is, preferably, an amount effective in controlling or reducing the addictive behavior. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the addictive or other behavior characteristic of the disease and does not necessarily indicate a total elimination of all disease symptoms.

The term "therapeutically effective amount" is further meant to define an amount resulting in the improvement of any parameters or clinical symptoms. The

actual dose may vary with each patient.

As used herein, the term "subject" or "patient" refers to a warm blooded animal, including but not limited to humans, such as a mammal which is afflicted with a particular disease state.

A therapeutically effective amount of the compound used in the treatment described herein can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

Preferred amounts and modes of administration are able to be determined by one skilled in the art. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disease state to be treated, the stage of the disease, and other relevant circumstances using formulation technology known in the art, described for example in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co.

Pharmaceutical compositions can be manufactured utilizing techniques known in the art. Typically the therapeutically effective amount of the compound will be admixed with a pharmaceutically acceptable carrier.

The compounds or compositions of the present invention may be administered by a variety of routes, for example, by enteral, oral, buccal, rectal, vaginal, dermal, nasal, bronchial, tracheal, pulmonary, parenteral, subcutaneous, intravenous, intramuscular, or intraperitoneal route, by injection, ingestion, or inhalation, for example.

A particularly preferred route of administration includes sustained release formulations, extended release formulations, or long acting formulations, that permit

delivery, such as substantially continuous delivery of drug over an extended period of time, such as greater than one, two, three, four or more weeks. A four week release is preferred.

For oral administration, the compounds can be formulated, for example, in a solid, such as capsules, pills, tablets, lozenges, melts, powders, or in a form for mixing into a solution, suspension or emulsion.

In another embodiment, the compounds of this invention can be tabletted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent which may also contain suspending agents, sweetening agents, flavoring agents, and preservative agents as are known in the art.

For parenteral administration the compounds may be dissolved in a physiologically acceptable pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers include water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, and buffers as are known in the art.

The compounds of this invention can also be administered topically. This can be accomplished by simply preparing a solution of the compound to be administered, preferably using a solvent known to promote transdermal absorption such as ethanol or dimethyl sulfoxide (DMSO) with or without other excipients. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety.

For surgical implantation, the active ingredients may be combined with any of the well-known biodegradable and bioerodible carriers, such as polylactides and poly-lactide-co-glycolides and collagen formulations. Such materials may be in the form of solid implants, sponges, and the like. In any event, for local use of the materials, the active ingredients usually be present in the carrier or excipient in a

weight ratio of from about 1:1000 to 1:20,000, but are not limited to ratios within this range.

Preferably, the compounds are in an extended release formulation. Extended (also referred to as sustained or controlled release) preparations may be achieved through the use of polymers (preferably poly-lactide or poly-lactide-co-glycolide polymers) to entrap or encapsulate the naltrexone described herein. Extended release formulations can be made by spray drying polymer-drug mixtures, emulsion-based technologies, coacervation based technologies, film casting, extrusion based technologies and other processes to manufacture polymer-drug microparticles possessing an extended release profile. Examples of suitable extended release technologies that can be used to incorporate the novel naltrexone forms described herein include, without limitation, the MEDISORB® technology, as described in, for example, US Patent Nos. 6,264,987 to Wright, 5,654,008 and/or 5,792,477, for example; the PROLEASE® technology, as described, for example in US Patent 6,358,443 to Herbert; the technologies described by Southern Research Institute, as described for example in US Patent 6,306,425; and "Method of Preparing Sustained Release Microparticles," U.S. Application No. 60/441,946, filed January 23, 2003, and the technologies described by Alza Corp., including the ALZAMER® Depot injection technology. The contents of these patents are incorporated herein by reference in their entirety.

In a preferred embodiment, the extended release formulation delivers therapeutically beneficial amounts of naltrexone to the patient for a period of at least one week, preferably at least about two weeks, more preferably at least about 3 or about 4 or more weeks.

In one preferred embodiment, the naltrexone is present in the extended release device or formulation in an amount of at least about 5% by weight, preferably at least about 10% by weight, more preferably at least about 30% by weight of the total weight of the device, or formulation. In one embodiment, the theoretical drug load is not 35% (or actual drug load of 40%, 45.8% or 26.1% load) by weight of the total sustained release device. However, in a preferred embodiment, the theoretical drug load is 35% total naltrexone.

It has been discovered that controlling the crystallinity of the total amount of naltrexone has a substantial impact upon the duration of release. For example, a composition containing PLGA microspheres, as described herein, characterized by total % naltrexone crystallinity between about 9-12% in a PLGA microsphere possesses a superior release profile of about 4 weeks. Lowering the % crystallinity can quicken the release. Thus, a composition containing PLGA microspheres, as described herein, characterized by total % naltrexone crystallinity of between about 4-9% in a PLGA microsphere possesses a superior release profile of less than 4 weeks, e.g. about 2 weeks. Likewise, a composition containing PLGA microspheres, as described herein, characterized by total % naltrexone crystallinity of about 12% or more in a PLGA microsphere possesses a superior release profile of at least 4 weeks, e.g. about 8 weeks. Such a substantial impact upon the duration of release, based on the % crystallinity was unexpected.

Alternatively, instead of incorporating naltrexone into polymeric particles, it is possible to entrap these materials in microparticles prepared. For example, coacervation techniques, interfacial polymerization (for example, hydroxymethylcellulose or gelatine-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), colloidal drug delivery systems (for example, liposomes, albumin, microparticles, microemulsions, nanoparticles, and nanocapsules), or macroemulsion systems can be used.

When the composition is to be used as an injectable material, including but not limited to needle-less injection, it can be formulated into a conventional injectable carrier. Suitable carriers include biocompatible and pharmaceutically acceptable solutions.

Method for manufacturing extended release devices

The invention includes a preferred method for manufacturing extended release devices, wherein the resulting device contains preferred mixtures of the described polymorphic forms.

Polymer solution can be formed by dissolving a poly(lactide)-co-glycolide polymer, such as a 75:25 DL PLGA (poly(lactide)-co-glycolide) in a polymer solvent, such as ethyl acetate (EtAc), to form a solution. Preferred PLGA polymers

are high molecular weight polymers, such as polymers possessing a molecular weight of at least about 100,000 daltons. A naltrexone solution can be formed by dissolving naltrexone base in a suitable solvent, such as one of the solvents described above, including benzyl alcohol (BA), to form a solution. The polymer solution and the naltrexone solution are preferably mixed together to form a drug/polymer solution that will be the "organic" or "oil" phase of the emulsion.

The "aqueous" or "continuous" phase of the emulsion (emulsifying solution) is prepared. The aqueous phase preferably contains poly(vinyl alcohol) (PVA) and polymer solvent, such as EtAc. The organic phase and the aqueous phase can be conveniently combined in a first static mixer to form an oil-in-water emulsion.

In an optional partial extraction step, the emulsion flows out of the first static mixer and into a second static mixer where the emulsion can be combined with a primary extraction solution which enters the second static mixer. The primary extraction solution (such as can be formed by an EtAc aqueous solution) can initiate solvent extraction from the microdroplets of the emulsion during the partial primary extraction step in the second static mixer.

The outflow of the first or second static mixer can flow into an extraction vessel containing primary extraction solution. The solvents (BA and EtAc) are substantially extracted from the organic phase of the emulsion in this primary solvent extraction step, resulting in nascent microparticles comprised mainly of polymer and drug. The primary solvent extraction step lasts for approximately six hours.

The microparticles can be collected, and vacuum dried, optionally with a nitrogen bleed using a customized vibratory sieve. After collection and prior to drying, the microparticles are rinsed with a 25% ethanol solution that removes the emulsifying agent (PVA), and enhances yield by aiding in the transfer of the microparticles to the cold dryer. This step is conducted, preferably at cold temperatures, until the desired level of dryness is achieved. As can be seen in the examples below, the degree of dryness (as measured, for example, by a humidity probe) impacts the degree of crystallinity achieved in the final product. For example, it can be advantageous to select a drying time of at least about 8, 16, 24 or 40 hours of drying. For example, it can be advantageous to select a drying time of at

least about 8, 16, 24 or 40 hours where drying is 40%, 70%, 95% or 100% complete respectively. Drying is considered complete when the absolute humidity of the effluent gas reaches approximately 0 g/m^3.

The microparticles can then be resuspended in a second extraction solution. The second solution can contain the solvent desired to form the polymorphic form, such as ethanol. For example, a solution comprising at least about 10% ethanol by volume, preferably at least about 20% ethanol by volume can be used. This can be conveniently called the reslurry and secondary solvent extraction steps. The solvent, such as ethanol, can facilitate further extraction of BA and EtAc. Further, the crystallinity of the drug increases during the step. The secondary solvent extraction step is carried out in an extraction vessel for approximately two, three, four or more hours. This step can be conveniently completed at room temperature. However, other temperatures can be selected as well. In the collection/final dry step, the microparticles are collected, and vacuum dried with a nitrogen bleed using a customized vibratory sieve.

In the final harvest step, the microparticles can be transferred into a sterile container and stored, for example, in a freezer at -20°C, until filling into vials. Preferably, the stored microparticles are sieved through a 150 micron screen to remove any oversized material prior to filling into vials.

Exemplification

Example 1.

The following solvates were made as described below. Thereafter the resulting precipitated material was analyzed using the analytical techniques described above, that is, X-ray powder diffraction, differential scanning calorimetry and infrared attenuated total reflectance (IR-ATR) detection mode.

Acetonitrile [XRPD = Figure 1; DSC = Figure 13; IR-ATR = Figure 25]
Crystallization out of this solvent yields an anhydrous form. Some variability in XRPD powder pattern is noted for substances obtained by fast and slow cooling, but the characteristic peaks are noted at the same scattering angles. This phase is characterized by a DSC melting transition having a temperature maximum of 175°C.

Dimethyl formamide [XRPD = Figure 2; DSC = Figure 14; IR-ATR = Figure 26] Crystallization out of this solvent yields the DMF solvate, which is characterized by a DSC desolvation transition having a temperature maximum of 113°C. The XRPD powder patterns of substances obtained by fast and slow cooling differs, and the fast cooling sample contains additional peaks not observed in the powder pattern of the slow cooling sample. The desolvation of the material obtained by slow cooling yielded an amorphous material that did not recrystallize to a form capable of exhibiting a melting endotherm. This property is most likely characteristic of the DMF solvate. The fast cooling sample exhibited a second endothermic transition, having a DSC melting transition maximum at 167°C, which is most likely due to the presence of the second phase in the fast cooling sample.

Water [XRPD = Figure 3; DSC = Figure 15; IR-ATR = Figure 27] Crystallization out of this solvent yields a hydrate, which is largely characterized by a DSC desolvation transition having a temperature maximum of 99°C. The dehydration of this hydrate yields detectable recrystallization phenomena, forming an anhydrous form having a DSC melting transition maximum at 160°C. During its melting transition, this form undergoes another crystallization transition, yielding the anhydrous form characterized by a DSC melting transition that has a temperature maximum of 175°C.

Methanol [XRPD = Figure 4; DSC = Figure 16; IR-ATR = Figure 28] Crystallization out of this solvent yields a methanol solvate. The XRPD powder patterns of substances obtained by fast and slow cooling differ, with the slow cooling sample containing additional peaks not observed in the powder pattern of the fast cooling sample. Interestingly, this difference does not carry over into the DSC of the two materials. Both samples were characterized by a DSC desolvation transition having a temperature maximum of 108°C, followed by well-defined melting/crystallization/melting phenomena at temperatures of 160°C, 162°C, and 175°C, respectively.

Ethanol [XRPD = Figure 5; DSC = Figure 17; IR-ATR = Figure 29]
Crystallization out of this solvent yields an ethanol solvate. The XRPD powder patterns of substances obtained by fast and slow cooling differ substantially, with the fast cooling sample containing additional peaks not observed in the powder pattern of the slow cooling sample. The DSC thermogram of the slow cooling sample is characterized by a desolvation transition having a temperature maximum of 120°C, eventually followed by a melting/crystallization/ melting sequence at temperatures of 160°C, 161°C, and 175°C, respectively. The DSC of the fast cooling sample contains a prominent desolvation endotherm having a temperature maximum of 92°C, which is most likely due to the presence of water having condensed in the sample during its crystallization. The temperature of this endotherm differs from that of the authentic hydrate, and may represent the formation of a mixed hydrate/ethanol polymorph.

Benzyl Alcohol [XRPD = Figure 6; DSC = Figure 18; IR-ATR = Figure 30]
Crystallization out of this solvent yields a benzyl alcohol solvate. This polymorph is largely characterized by a DSC desolvation transition having a temperature maximum of 124°C. The dehydration of this hydrate yields weak, but detectable, recrystallization phenomena, forming anhydrous forms having DSC melting transition maxima at 153°C and 160°C.

Dichloromethane [XRPD = Figure 7; DSC = Figure 19; IR-ATR = Figure 31]
Crystallization out of this solvent yields a dichloromethane solvate. The XRPD powder patterns of substances obtained by fast and slow cooling appear to be completely different, although the powder pattern of the fast cooling sample strongly resembles the powder patterns of the two anhydrous materials crystallized out of acetonitrile. The DSC thermogram of the slow cooling sample is largely characterized by a melting transition having a peak maximum at 176°C. Comparison of all of the data indicates that this anhydrous form is the same anhydrous form as had been crystallized out of acetonitrile. The DSC of the slow cooling sample contains a prominent desolvation endotherm having a temperature maximum of 90°C, which is most likely due to the presence of water having

condensed in the sample during its crystallization. The temperature of this endotherm differs from that of the authentic hydrate, and may represent the formation of a mixed hydrate/dichloromethane polymorph. The apparent co-crystallization of the hydrate represents the origin of the differences noted in the two sets of powder patterns for materials crystallized out of dichloromethane.

Acetone [XRPD = Figure 8; DSC = Figure 20; IR-ATR = Figure 32]
Crystallization out of this solvent yields an acetone solvate. The XRPD powder patterns of substances obtained by fast and slow cooling exhibit differences in relative intensities (probably associated with preferential orientation), but the overall pattern of scattering angles is fairly comparable between the two. The DSC thermograms of the two samples are also quite similar, being characterized by a desolvation transition having a temperature maximum of 138°C, and eventually followed by a melting endotherm at a temperature 176°C. Prior to the large melting endotherm (temperature around 160°C), there is a weak melt/recrystallization endotherm as well.

Ethyl Acetate [XRPD = Figure 9; DSC = Figure 21; IR-ATR = Figure 33]
Crystallization out of this solvent yields an ethyl acetate solvate. The XRPD powder patterns of substances obtained by fast and slow cooling differ substantially. The DSC thermogram of both polymorphs is characterized by a desolvation transition having a temperature maximum of 123°C, eventually followed by a melting/crystallization/ melting sequence at temperatures of 161°C, 162°C, and 176°C, respectively. The DSC of the fast cooling sample also contains a prominent desolvation endotherm having a temperature maximum of 91°C, which is most likely due to the presence of water having condensed in the sample during its crystallization. The temperature of this endotherm differs from that of the authentic hydrate, and may represent the formation of a mixed hydrate/ethyl acetate polymorph.

Methyl Ethyl Ketone [XRPD = Figure 10; DSC = Figure 22; IR-ATR = Figure 34]
Crystallization out of this solvent yields an anhydrous form. The XRPD powder

patterns of substances obtained by fast and slow cooling are quite similar, and each strongly resembles the powder patterns of the anhydrous materials crystallized out of acetonitrile. The DSC thermogram of the slow cooling sample contains an endothermic transition at very low temperatures, but is still dominated by the melting transition having a peak maximum at 176°C. The DSC of the fast cooling sample consists essentially of only the melting endotherm (maximum at 176°C).

Toluene [XRPD = Figure 11; DSC = Figure 23; IR-ATR = Figure 35]
Crystallization out of this solvent yields a toluene solvate. The XRPD powder patterns of substances obtained by fast and slow cooling exhibit a significant number of qualitative differences that are probably related to preferential orientation. The DSC thermograms of the two samples are also fairly similar, being characterized by a desolvation transition having a temperature maximum of 138°C, and eventually followed by a melting endotherm at a temperature of 176°C. Prior to the large melting endotherm (temperature around 160°C), there is a weak melt/recrystallization endotherm as well.

Hexane [XRPD = Figure 12; DSC = Figure 24; IR-ATR = Figure 36]
Crystallization out of this solvent yields a hexane solvate. The XRPD powder patterns of substances obtained by fast and slow cooling strongly resemble each other, and only differ in some of the relative intensities. The DSC thermogram of the sample obtained through the use of fast cooling is characterized by a desolvation transition having a temperature maximum of 114°C, and which is eventually followed by a melting/crystallization/ melting sequence at temperatures of 153°C, 158°C, and 174°C, respectively. The DSC of the slow cooling sample also contains a prominent desolvation endotherm having a temperature maximum of 91°C, which is most likely due to the presence of water having condensed in the sample during its crystallization. The temperature of this endotherm differs from that of the authentic hydrate, and may represent the formation of a mixed hydrate/ethyl acetate polymorph.

Example 2.

Preparation of naltrexone-containing microparticles

Formulation A

The naltrexone base microparticles were produced using a co-solvent extraction process. The theoretical batch size was 15 to 20 grams. The polymer (MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6536 DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio) 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 1/4" 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, 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 fifteen 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.

Example 3

A 1 kg batch of naltrexone microspheres were prepared as follows. Polymer solution was formed by dissolving 75:25 DL PLGA (poly(lactide)-co-glycolide) in ethyl acetate (EtAc) to form a solution of 16.7% polymer and 83.3% EtAc. A naltrexone solution was formed by dissolving naltrexone base in benzyl alcohol (BA) to form a solution of 30% naltrexone base anhydrous and 70% BA. The polymer solution and the naltrexone solution were mixed together to form a drug/polymer solution that was the "organic" or "oil" phase of the emulsion.

The "aqueous" or "continuous" phase of the emulsion (emulsifying solution) was prepared by dissolving poly(vinyl alcohol) (PVA) and EtAc in water-for-injection (WFI). The organic phase and the aqueous phase were combined in a first static mixer to form an oil-in-water emulsion. The droplet size of the emulsion was determined by controlling the flow rates of the two phases through the first static mixer.

In a partial primary extraction step, the emulsion flowed out of the first static mixer and into a second static mixer where the emulsion was combined with a Primary extraction solution which enters the second static mixer. The primary extraction solution (2.5% EtAc and 97.5% WFI at approximately 6°C) initiated solvent extraction from the microdroplets of the emulsion during the partial primary extraction step in the second static mixer.

The outflow of the second static mixer (combined flow stream of the emulsion and the primary extraction solution) flowed into an extraction vessel containing primary extraction solution. The solvents (BA and EtAc) were further extracted from the organic phase of the emulsion in this primary solvent extraction step, resulting in nascent microparticles comprised mainly of polymer and drug. The primary solvent extraction step lasted for approximately six hours.

The microparticles were collected, and vacuum dried with a nitrogen bleed using a customized vibratory sieve. After collection and prior to drying, the

microparticles were rinsed with a 25% ethanol solution that removes the emulsifying agent (PVA), and enhances yield by aiding in the transfer of the microparticles to the dryer.

To further reduce the solvent levels the microparticles were resuspended in a second extraction solution of 25% ethanol and 75% WFI in the reslurry and secondary solvent extraction steps. The ethanol facilitated further extraction of BA and EtAc. The secondary solvent extraction step was carried out in an extraction vessel for approximately four hours. In the collection/final dry step, the microparticles were collected, and vacuum dried with a nitrogen bleed using a second customized vibratory sieve.

In the final harvest step, the microparticles were transferred into a sterile container and stored in a freezer at -20°C until filling into vials. Preferably, the stored microparticles were sieved through a 150 micron screen to remove any oversized material prior to filling into vials.

Several lots of microspheres prepared by the method above were stored at various temperatures for varying periods of time. Table 3 below shows the percent crystallinity as determined by XRPD of each lot when stored for up 25 months at frozen, refrigerated and room temperature conditions. The results for each lot are within the tolerance levels of the methodology and demonstrate that the percent crystallinity of each lot remains stable over time.

Table 3.

Stability Lots—Percent Crystallinity (XRPD)				
Lot	Interval	Frozen -10°C	Refrigerated 4-8°C	Room Temp 25°C
1	25 months	14.2%	NA	14.0%
2	24 months	13.7%	13.8%	NA
3	20 months	13.1%	NA	14.9%
4	16 months	15.3%	NA	13.9%
5	15 months	7.6%	NA	8.5%
6	15 months	8.5%	NA	8.6%
7	10 months	16.0%	NA	14.6%
8	3 months	5.4%	NA	5.6%

NA= not available

X-ray powder diffraction

Twenty-one lots of naltrexone microparticles were prepared in accordance with the process described in Example 3 above to produce microparticles having a theoretical drug load of 35%. Each of the 21 lots was analyzed by x-ray powder diffraction (XRPD) using a Bruker D8 Advance XRD using 0.02°/step with a 1 second interval from 2.5° to 40° 2-theta. Percent crystallinity was determined by AUC subtraction of the amorphous halo and calculated as a ratio of the crystalline AUC to total AUC. Percent crystallinity is reported as percent of total microparticle rather than as percent of drug load. The lots contain approximately 35% drug load. Therefore, 10.5% crystallinity calculates to be 30% of the total drug load.

The x-ray powder patterns obtained for naltrexone anhydrous, monohydrate, benzyl alcohol solvate, and ethanolate polymorph forms were analyzed. Table 4 shows the approximate 2-theta angles used to initially identify each form. Figure 39 contains the x-ray powder pattern for one lot and identifies four forms. These data clearly indicate that the four forms are present in the microparticles.

Table 4: Identifying 2-theta angle for the naltrexone polymorphs

Polymorphic form	2-theta angle (approximate)
Anhydrous	8°
Monohydrate	7°
Benzyl alcohol solvate	5.5° or 5.6° and/or 7.3°
Ethanolate	8.1° and/or 9°

Table 5 displays the percent crystallinity (of total weight of the microparticles produced by the process) and relative percent distribution of each of the four polymorphic forms for the 21 lots. These data demonstrate that the relative ratio of the four polymorphic forms is generally consistent, regardless of the total crystallinity. These data further show that greater than about 55% of the naltrexone drug load is non-crystalline.

Table 5A

Lot Number	Percent Crystallinity	Benzyl Alcohol Solvate	Monohydrate	Anhydrous	Ethanolate
1	13.0	6.1	9.4	16.9	67.6
2	7.1	5.6	9.0	14.9	70.6
3	7.8	7.4	7.4	15.4	69.8
4	16.0	11.8	17.8	14.4	55.9
5	11.8	11.0	15.8	11.0	62.1
6	8.2	5.6	10.0	19.7	64.7
7	9.0	8.9	10.4	15.6	65.1
8	5.9	11.8	11.4	13.3	63.6
9	7.3	9.9	16.3	14.7	59.2
10	8.5	7.2	12.4	16.3	64.1
11	5.7	8.9	12.2	14.1	64.8
12	7.4	10.6	14.1	14.8	60.5
13	3.6	13.1	19.2	16.2	51.5
14	5.8	15.5	17.9	13.2	53.4
15	6.8	8.0	16.0	19.4	56.6
16	12.0	7.8	12.6	16.6	63.0
17	11.5	11.8	14.3	15.3	58.6
18	11.2	11.4	16.7	14.3	57.5
19	15.7	10.3	15.9	14.7	59.1
20	10.4	10.7	13.9	13.4	62.0
21	11.0	9.3	16.3	16.8	57.6
Mean	**9.3**	**9.7**	**13.8**	**15.3**	**61.3**
STD DEV	**3.3**	**2.6**	**3.3**	**2.0**	**5.0**
% RSD	**35.4**	**26.6**	**24.0**	**13.0**	**8.2**
Min	**3.6**	**5.6**	**7.4**	**11.0**	**51.5**
Max	**16.0**	**15.5**	**19.2**	**19.7**	**70.6**

Subsequently, a more comprehensive data analysis was conducted using the Bruker D8 Advance XRD and EVA software comparing the 2-theta angles and d-spacing from samples of the 4 polymorphs to the Vivitrex® microspheres. This analysis revealed that the 4 apparent identification peaks visually observed were actually 2 pairs of identification peaks from 2 polymorphs (benzyl alcohol solvate and ethanolate) and only these polymorphs were identifiable in the microspheres. The data for the above lots as well as additional lots is set forth in Table 5B.

Table 5B

Example	Scale	Percent Crystallinity (Of microsphere)	Percent Crystallinity (Of drug load)	Benzyl Alcohol Solvate (Percent of total crystallinity)	Ethanolate (Percent of total cystallinity)
1	1 kg	13.0	37.1	14.6	85.4
2	1 kg	7.1	20.3	15.6	84.4
3	1 kg	7.8	22.3	13.7	86.3
4	1 kg	16.0	45.7	28.9	71.1
5	1 kg	11.8	33.7	25.4	74.6
6	1 kg	8.2	23.4	13.6	86.4
7	1 kg	9.0	25.7	20.2	79.8
8	1 kg	5.9	16.9	22.8	77.2
9	1 kg	7.3	20.9	24.2	75.8
10	1 kg	8.5	24.3	13.2	86.8
11	1 kg	5.7	16.3	22.0	78.0
12	1 kg	7.4	21.1	22.1	77.9
13	1 kg	3.6	10.3	24.3	75.7
14	1 kg	5.8	16.6	33.4	66.6
15	1 kg	6.8	19.4	23.7	76.3
16	1 kg	12.0	34.3	19.1	80.9
17	1 kg	11.5	32.9	25.6	74.4
18	1 kg	11.2	32.0	27.0	73.0
19	1 kg	15.7	44.9	25.6	74.4
20	1 kg	10.4	29.7	23.0	77.0
21	1 kg	11.0	31.4	24.9	75.1
22	1 kg	7.6	21.7	17.4	82.6
23	1 kg	8.1	23.1	20.6	79.4
24	1 kg	5.3	15.1	10.4	89.6
25	1 kg	7.0	20.0	22.9	77.1
26	1 kg	9.8	28.0	16.9	83.1
27	1 kg	11.2	32.0	26.7	73.3
28	1 kg	13.0	37.1	17.3	82.7
29	1 kg	13.3	38.0	24.1	75.9
30	1 kg	8.1	23.1	16.0	84.0
31	1 kg	10.4	29.7	23.4	76.6
32	1 kg	8.4	24.0	21.7	78.3
33	1 kg	7.9	22.6	15.8	84.2
34	1 kg	8.8	25.1	26.3	73.7
35	1 kg	13.9	39.7	13.2	86.8
36	1 kg	6.8	19.4	10.9	89.1
37	1 kg	6.5	18.6	8.2	91.8
38	1 kg	12.9	36.9	21.1	78.9
39	1 kg	5.0	14.3	17.0	83.0

Example	Scale	Percent Crystallinity (Of microsphere)	Percent Crystallinity (Of drug load)	Benzyl Alcohol Solvate (Percent of total crystallinity)	Ethanolate (Percent of total cystallinity)
40	1 kg	7.2	20.6	0.0	100
41	1 kg	10.8	30.9	26.1	73.9
42	1 kg	12.9	36.9	32.0	68.0
43	1 kg	5.7	16.3	0.0	100.0
44	225 g	17.1	48.9	9.5	90.5
45	225 g	15.2	43.4	12.3	87.7
46	225 g	13.2	37.7	14.7	85.3
47	225 g	18.4	52.6	8.0	92.0
48	225 g	13.7	39.1	6.0	94.0
49	225 g	15.8	45.1	8.2	91.8
50	225 g	12.7	36.3	13.6	86.4
	Mean	**10.0**	**28.7**	**18.5**	**81.5**
	STD DEV	**3.6**	**10.2**	**7.6**	**7.6**
	Min	**3.6**	**10.3**	**0.0**	**66.6'**
	Max	**18.4**	**52.6**	**33.4**	**100.0**

The process was repeated employing different drying times for the "first dry". The percent crystallinity reported for each run is reported in the following table and Fig. 38.

Table 6 Effect of Dryness (1st Dry) on Drug Product Crystallinity

Batch #	Time of Dry, Hours	% Completeness Of Drying	% Crystallinity of Microparticle
02-017-076 E1	8	43.7%	3.7
02-017-076 E2	16	76.6%	4.6%
02-017-076 E3	24	98.8%	6.4%
02-017-076 E4	40	100%	16.1%

Completeness of drying is defined as the ratio of the AUC of the effluent gas absolute humidity over time up to a specified time to the AUC of the absolute humidity over time up to the final time point (i.e., time at which absolute humidity reaches 0 g/m^3.

Modifications and variations of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A polymorphic form of naltrexone ethanolate characterized by an X-ray powder diffraction with a characteristic peak at about 9° (2θ).

2. A polymorphic form according to Claim 1 further characterized by the X-ray powder diffraction pattern of Figure 5A.

3. A polymorphic form according to Claim 1 further characterized by the DSC pattern of Figure 17A.

4. A polymorphic form according to Claim 1 further characterized by the IR-ATR of Figure 29A.

5. A polymorphic form according to Claim 1 further characterized by the X-ray powder diffraction pattern of Figure 5B.

6. A polymorphic form according to Claim 1 further characterized by the DSC pattern of Figure 17B.

7. A polymorphic form according to Claim 1 further characterized by the IR-ATR of Figure 29B.

8. A polymorphic form according to Claim 1 wherein the form is in the substantial absence of a polymorphic form of naltrexone selected from the group consisting of: naltrexone benzyl alcohol solvate, naltrexone monohydrate, and anhydrous naltrexone.

9. A polymorphic form according to Claim 1 where the form is in the absence of naltrexone benzyl alcohol solvate.

10. A polymorphic form according to Claim 1 wherein the form is substantially pure.

11. A polymorphic form according to Claim 1 in admixture with one or more distinct polymorphic forms and/or a non-crystalline naltrexone.

12. A polymorphic form according to Claim 11 wherein the non-crystalline naltrexone is dissolved naltrexone.

13. A polymorphic form of naltrexone benzyl alcohol solvate which is characterized by an X-ray powder diffraction with a characteristic peak at about 5-6° (2θ).

14. A polymorphic form according to Claim 13 which is characterized by the X-ray powder diffraction pattern of Figure 6.

15. A polymorphic form of Claim 13 further characterized by the DSC pattern of Figure 18.

16. A polymorphic form of Claim 13 further characterized by the IR-ATR of Figure 30.

17. A polymorphic form of naltrexone dimethylformamide solvate which is characterized by an X-ray powder diffraction pattern of Figure 2.

18. A polymorphic form of Claim 17 further characterized by the DSC pattern of Figure 14.

19. A polymorphic form of Claim 17 further characterized by the IR-ATR of Figure 26.

20. A polymorphic form of naltrexone methanol solvate which is characterized by the X-ray powder diffraction pattern of Figure 4.

21. A polymorphic form of Claim 20 further characterized by the DSC pattern of Figure 16.

22. A polymorphic form of Claim 20 further characterized by the IR-ATR of Figure 28.

23. A polymorphic form of naltrexone dichloromethane which is characterized by the X-ray powder diffraction pattern of Figure 7.

24. A polymorphic form of Claim 23 further characterized by the DSC pattern of Figure 19.

25. A polymorphic form of Claim 23 further characterized by the IR-ATR of Figure 31.

26. A polymorphic form of naltrexone acetone solvate which is characterized by the X-ray powder diffraction pattern of Figure 8.

27. A polymorphic form of Claim 26 further characterized by the DSC pattern of Figure 20.

28. A polymorphic form of Claim 26 further characterized by the IR-ATR of Figure 32.

29. A polymorphic form of naltrexone ethylacetate solvate which is characterized by the X-ray powder diffraction pattern of Figure 9.

30. A polymorphic form of Claim 29 further characterized by the DSC pattern of Figure 21.

31. A polymorphic form of Claim 29 further characterized by the IR-ATR of Figure 33.

32. A polymorphic form of naltrexone toluene solvate which is characterized by the X-ray powder diffraction pattern of Figure 11.

33. A polymorphic form of Claim 32 further characterized by the DSC pattern of Figure 23.

34. A polymorphic form of Claim 32 further characterized by the IR-ATR of Figure 35.

35. A polymorphic form of naltrexone hexane solvate which is characterized by the X-ray powder diffraction pattern of Figure 12.

36. A polymorphic form of Claim 35 further characterized by the DSC pattern of Figure 24.

37. A polymorphic form of Claim 35 further characterized by the IR-ATR of Figure 36.

38. A method of making a polymorphic form of naltrexone comprising:
(i) mixing a naltrexone base anhydrous or a naltrexone salt with a solvent or solvent system selected from the group consisting of acetonitrile, dimethyl formamide, water, methanol, ethanol, benzyl alcohol, dichloromethane, acetone, ethyl acetate, methyl ethyl ketone, toluene and hexane and combinations thereof; (ii) heating the mixture to prepare a nearly saturated solution; (iii) cooling the nearly saturated solution to room temperature at a rate not greater than 1-2°C/min thereby forming the polymorphic form; and (iv) harvesting the polymorphic form.

39. A method of Claim 38 wherein the polymorphic form is characterized by the X-ray powder diffraction (2θ) pattern selected from the group consisting of Figures 1A, 2A, 4A, 5A, 7A, 8A, 9A ,10A, 11A, and 12A.

40. The method of Claim 39 wherein the polymorphic form is characterized by the DSC pattern selected from the group consisting of Figures 13A, 14A, 16A, 17A, 19A, 20A, 21A, 22A, 23A and 24A.

41. The method of Claim 39 wherein the polymorphic form is characterized by the IR-ATR selected from the group consisting of Figures 25A, 26A, 28A, 29A, 31A, 32A, 33A, 34A, 35A, and 36A.

42. A method of making a polymorphic form of naltrexone comprising: (i) mixing a naltrexone base anhydrous or a naltrexone salt with a solvent or solvent system selected from the group consisting of acetonitrile, dimethyl formamide, water, methanol, ethanol, benzyl alcohol, dichloromethane, acetone, ethyl acetate, methyl ethyl ketone, toluene and hexane and combinations thereof; to form a mixture; (ii) heating the mixture to prepare a nearly saturated solution; (iii) cooling the nearly saturated solution to room temperature as rapidly as possible thereby forming the polymorphic form; and (iv) harvesting the polymorphic form.

43. The method of Claim 42 wherein the polymorphic form is characterized by the X-ray powder diffraction (2θ) pattern selected from the group consisting of Figures 1B, 2B, 3, 4B, 5B, 6, 7B, 8B, 9B ,10B, 11B, and 12B.

44. The method of Claim 42 wherein the polymorphic form is characterized by the DSC pattern selected from the group consisting of Figures 13B, 14B, 15, 16B, 17B, 18, 19B, 20B, 21B, 22B, 23B and 24B.

45. The method of Claim 42 wherein the polymorphic form is characterized by the IR-ATR selected from the group consisting of Figures 25B, 26B, 27, 28B, 29B, 30, 31B, 32B, 33B, 34B, 35B, and 36B.

46. A composition comprising at least 35% by weight naltrexone wherein the naltrexone is characterized by at less than about 45% crystallinity in a non-crystalline state.

47. A naltrexone composition comprising a naltrexone ethanolate according to Claim 1 and wherein at least about 10% by weight of the total naltrexone is crystalline.

48. A composition according to Claim 47 wherein at least about 20% by weight of the naltrexone is crystalline.

49. A composition according to Claim 47 wherein at least about 30% by weight of the naltrexone is crystalline.

50. A composition according to Claim 47 wherein between about 30 and 70% by weight of the naltrexone is crystalline.

51. A composition according to Claim 47 wherein the remaining naltrexone comprises an amorphous naltrexone.

52. A composition according to Claim 47 wherein the remaining naltrexone comprises dissolved naltrexone.

53. A composition of Claim 47 wherein at least about 40% of the crystalline naltrexone is naltrexone ethanolate.

54. A composition of Claim 47 wherein the crystalline naltrexone is in the substantial absence of a polymorphic form of naltrexone selected from the group consisting of: naltrexone benzyl alcohol solvate, naltrexone monohydrate, and anhydrous naltrexone.

55. A composition of Claim 47 further comprising one or two polymorphic forms selected from the group consisting of naltrexone benzyl alcohol solvate, naltrexone monohydrate, and anhydrous naltrexone.

56. A composition of Claim 47 further comprising a pharmaceutically acceptable carrier.

57. A composition of Claim 56 wherein the composition is an extended release formulation.

58. A composition of Claim 57 wherein the pharmaceutically acceptable carrier comprises a poly-lactide-co-glycolide.

59. A composition of Claim 56 wherein the polymorphic form is not Formulation A.

60. A composition according to Claim 57 wherein the polymorphic form is produced during the manufacturing process for said extended release formulation.

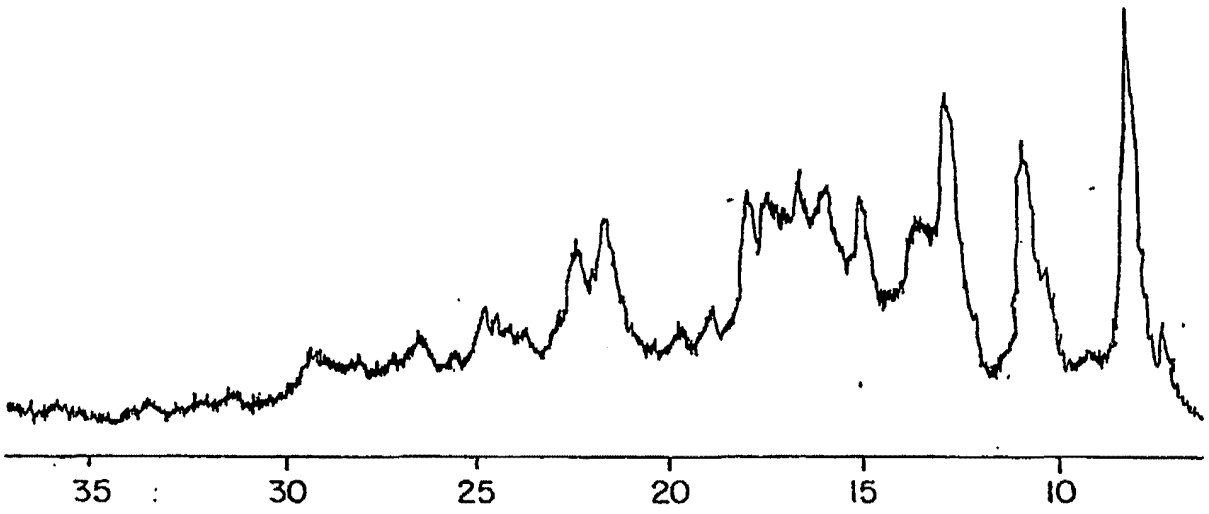


FIG. 1A

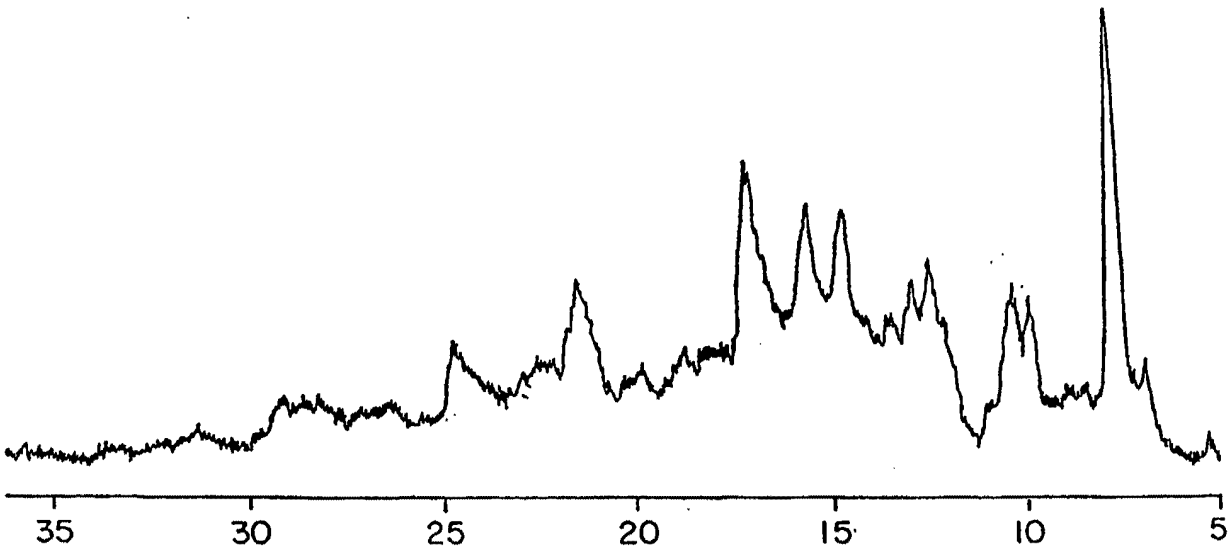


FIG. 1B

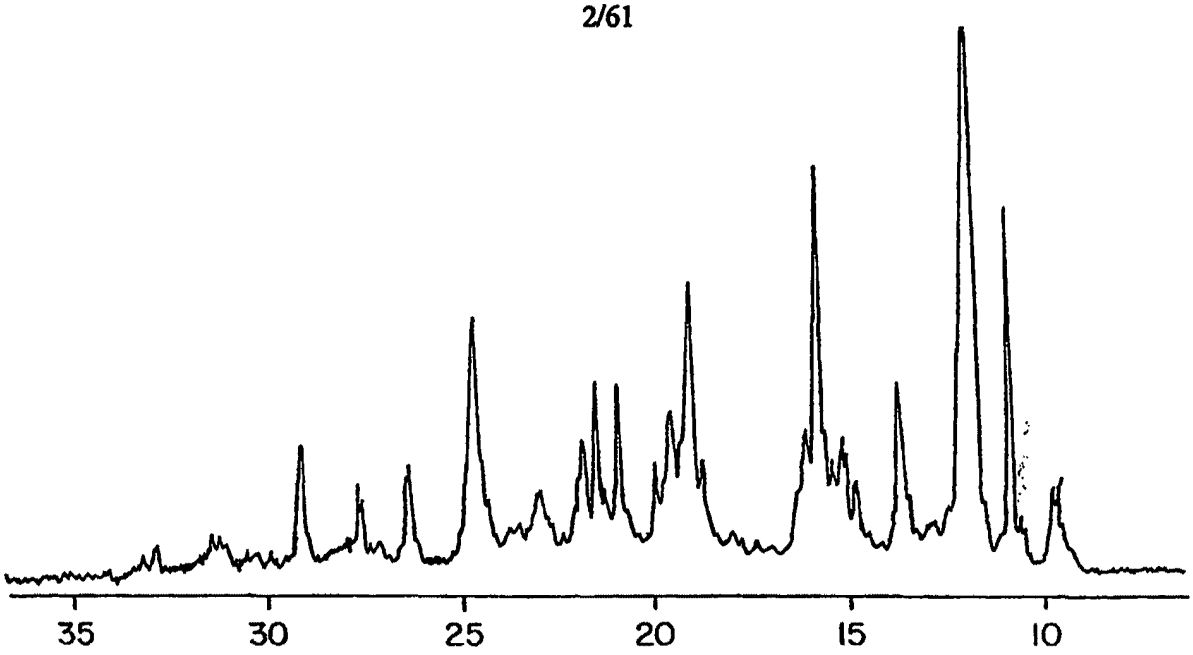


FIG. 2A

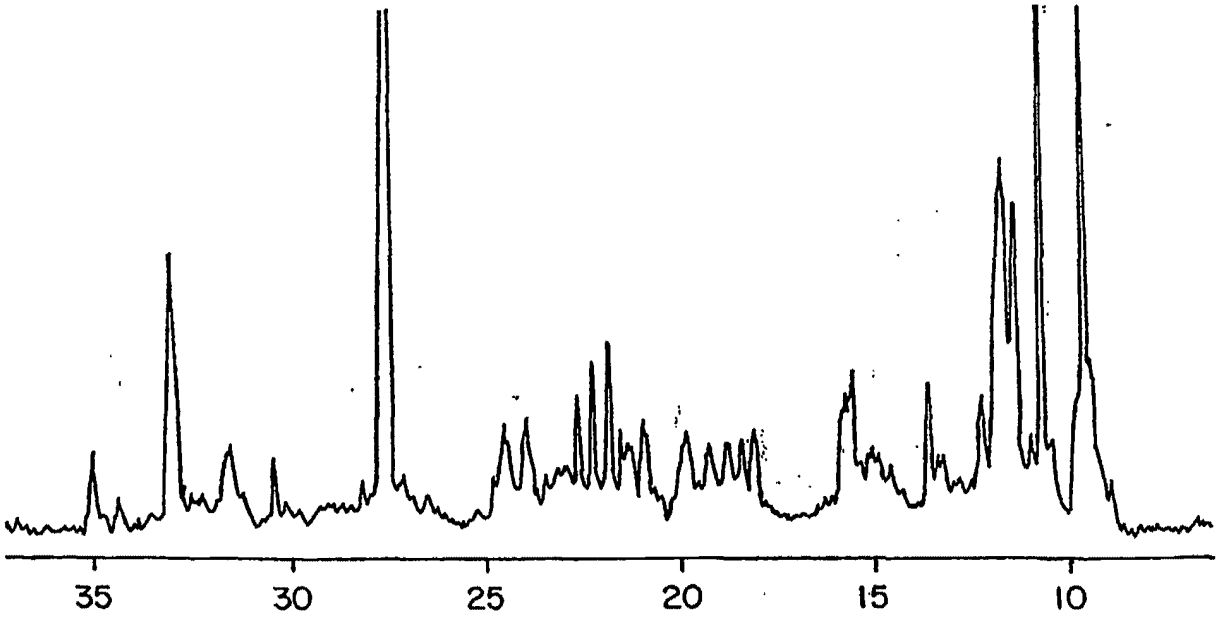


FIG. 2B

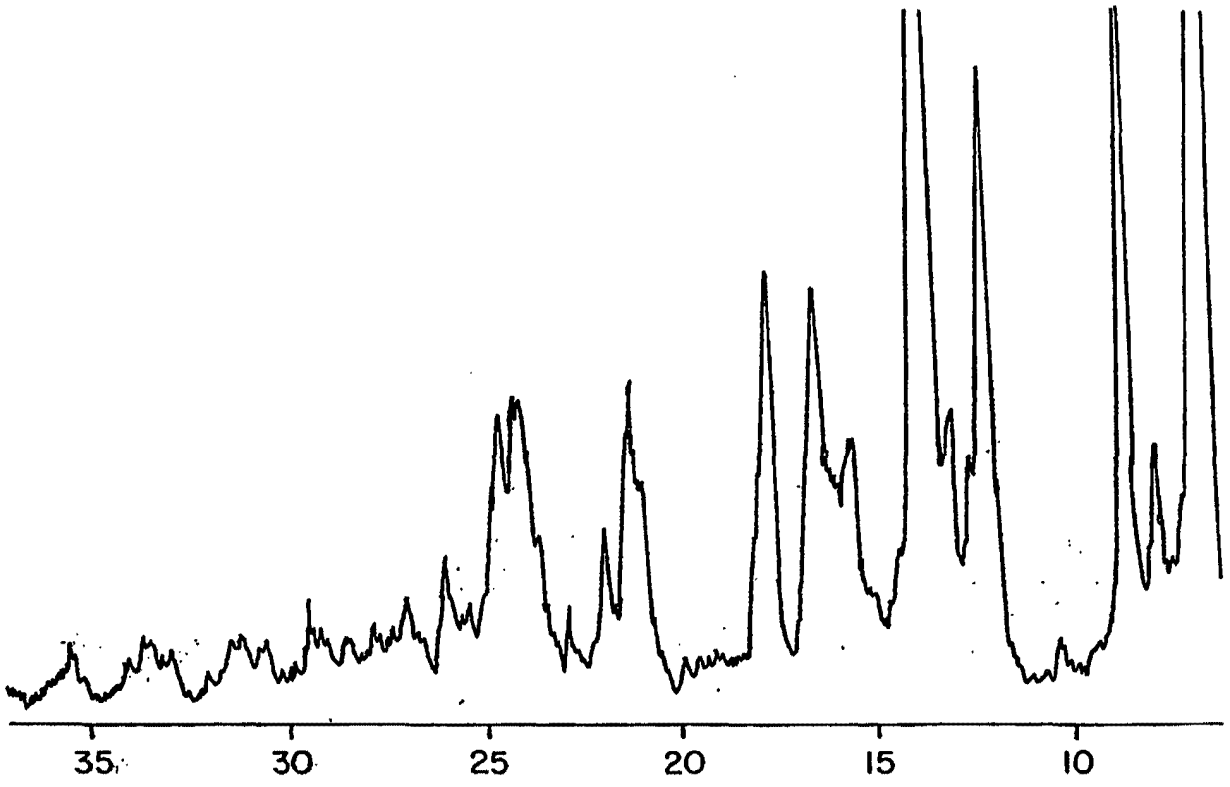


FIG. 3

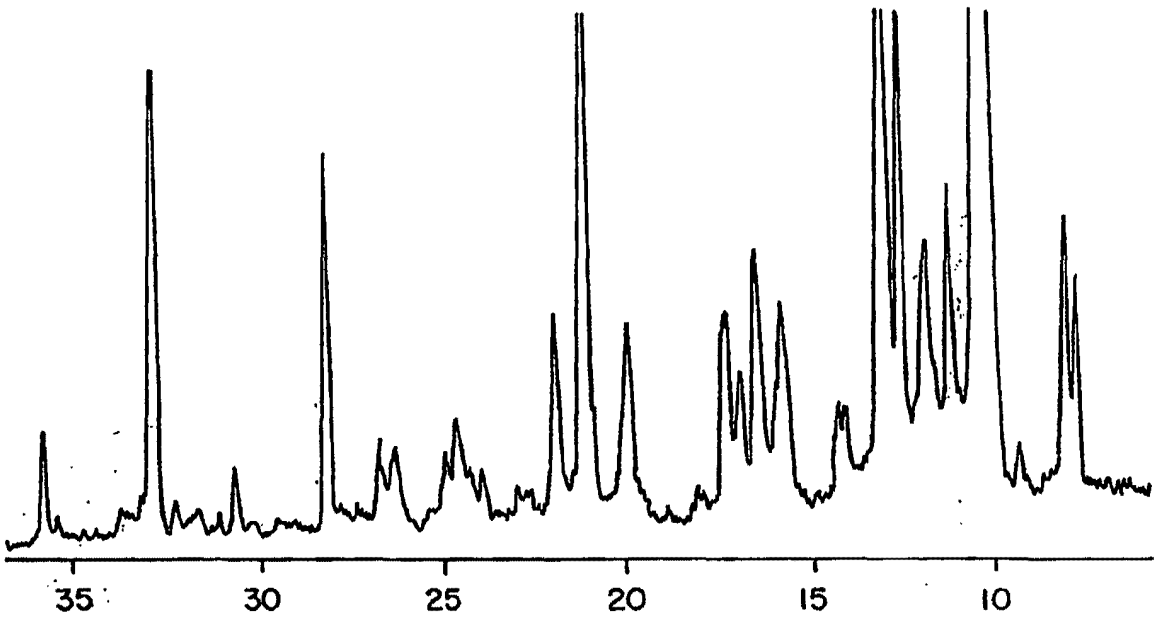


FIG. 4A

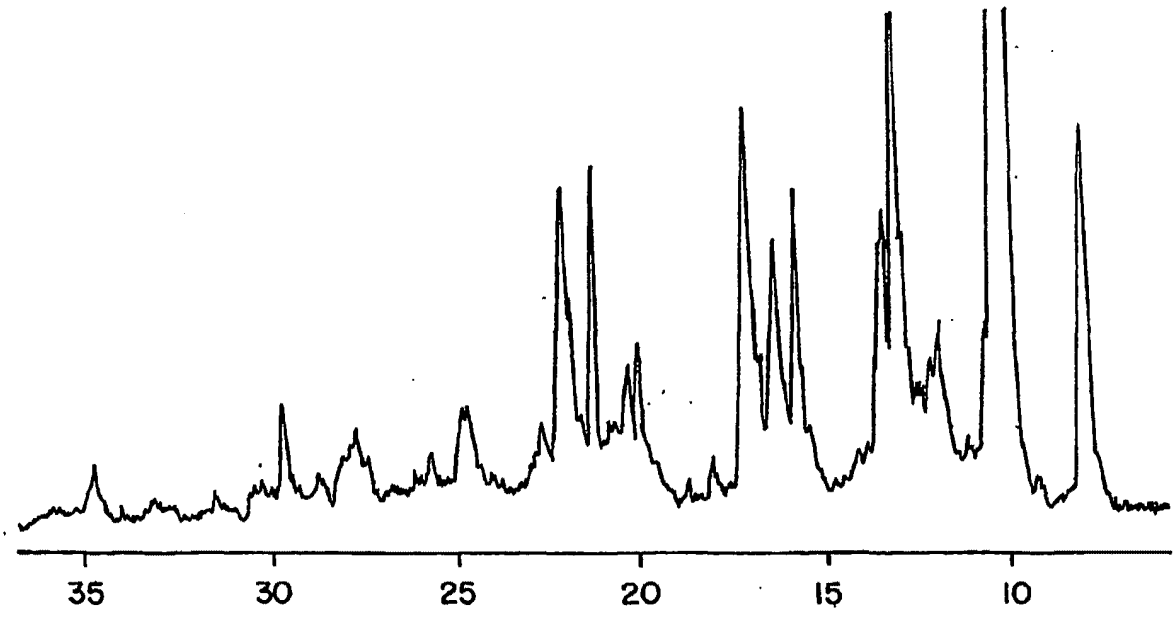


FIG. 4B

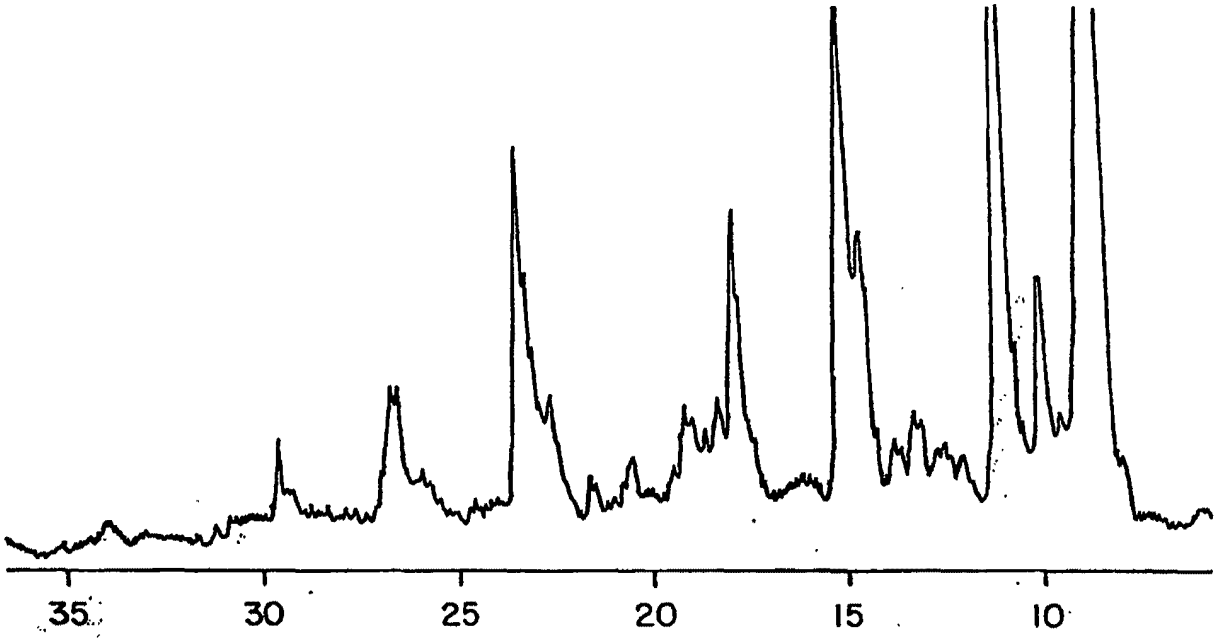


FIG. 5A

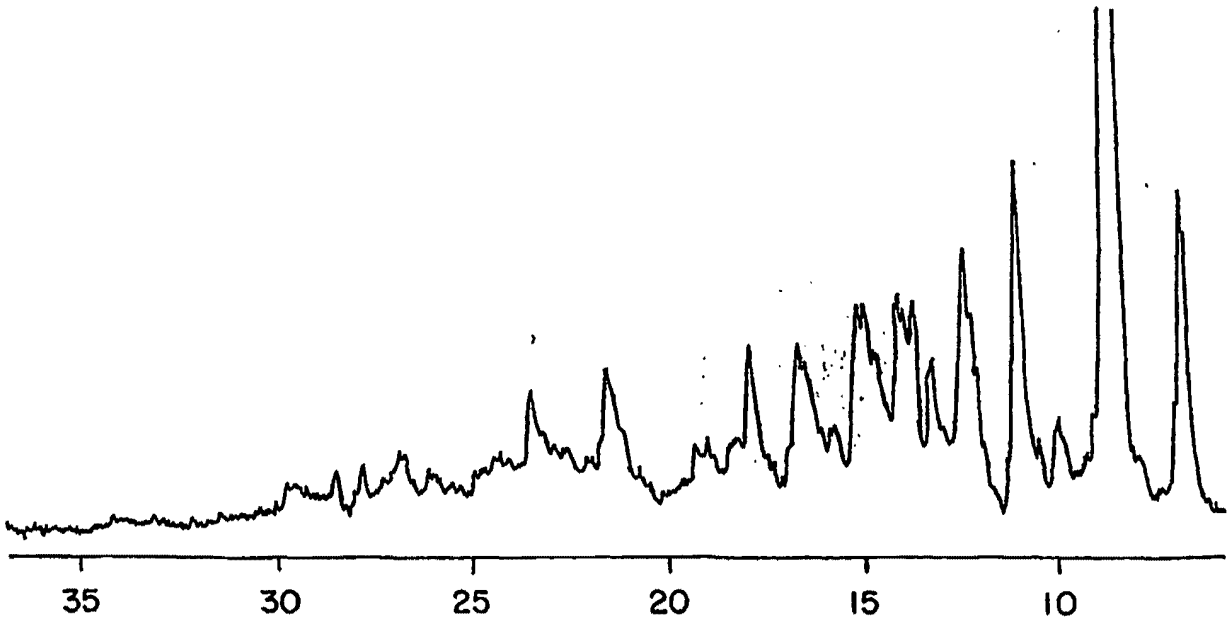


FIG. 5B

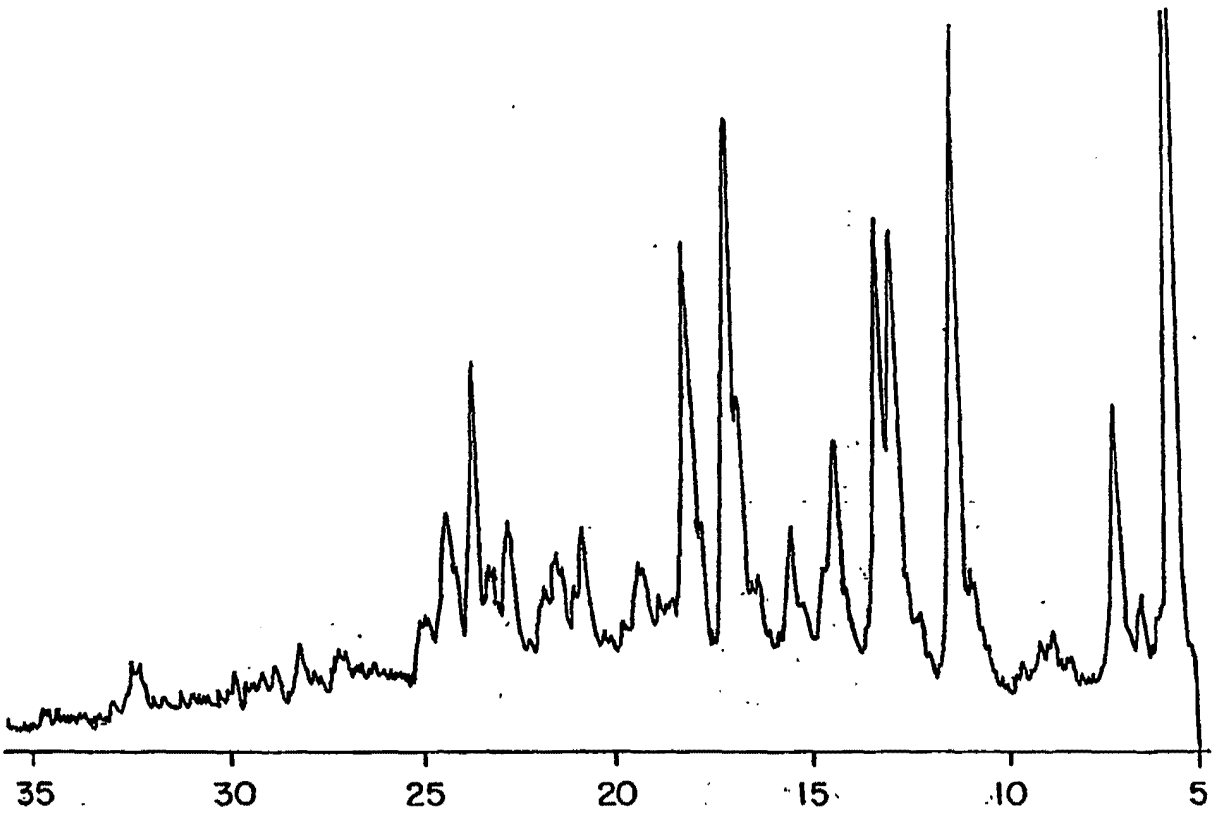


FIG. 6

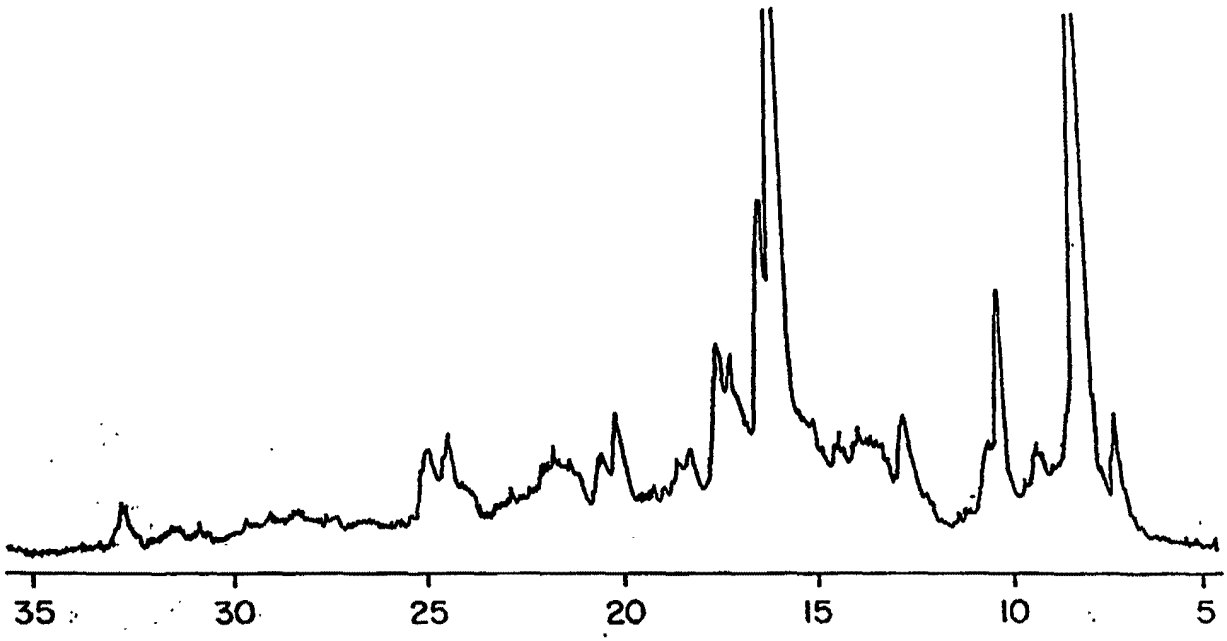


FIG. 7A

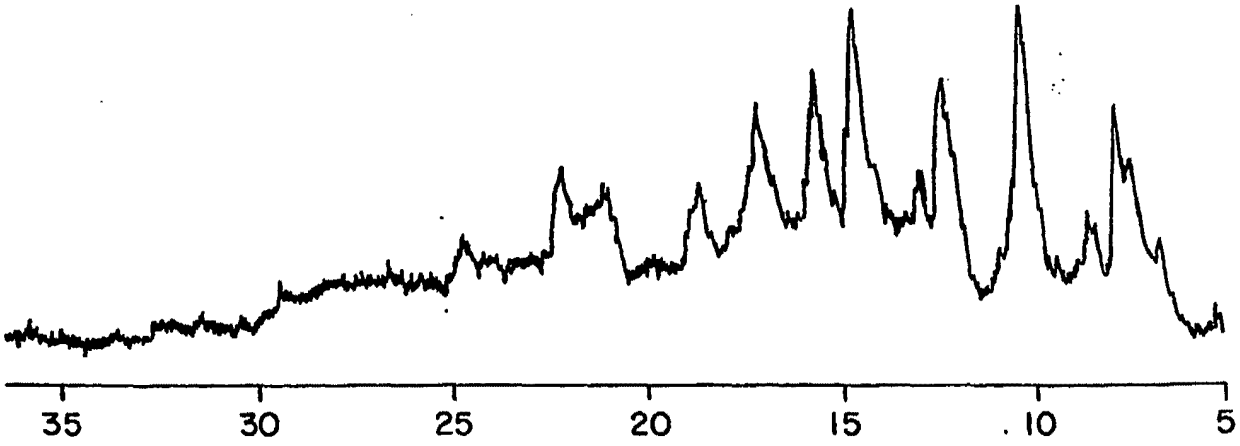


FIG. 7B

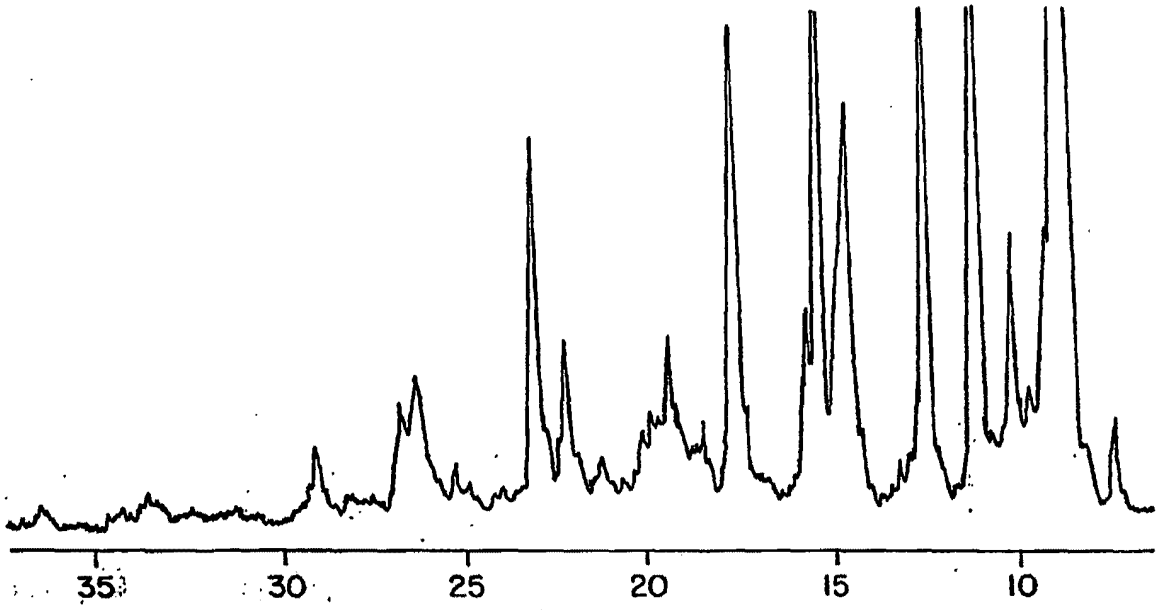


FIG. 8A

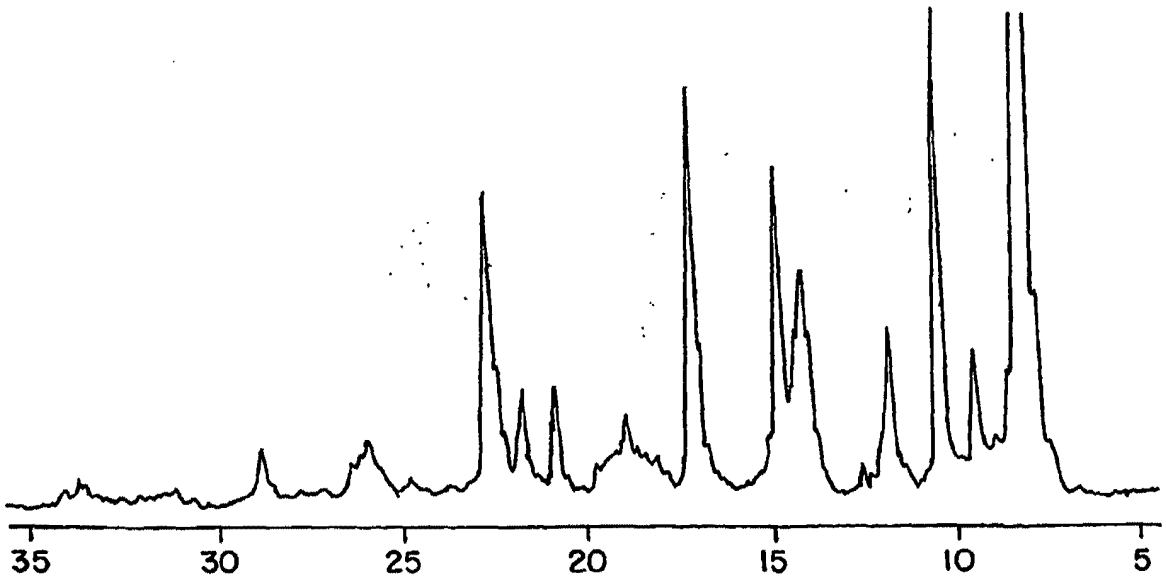


FIG. 8B

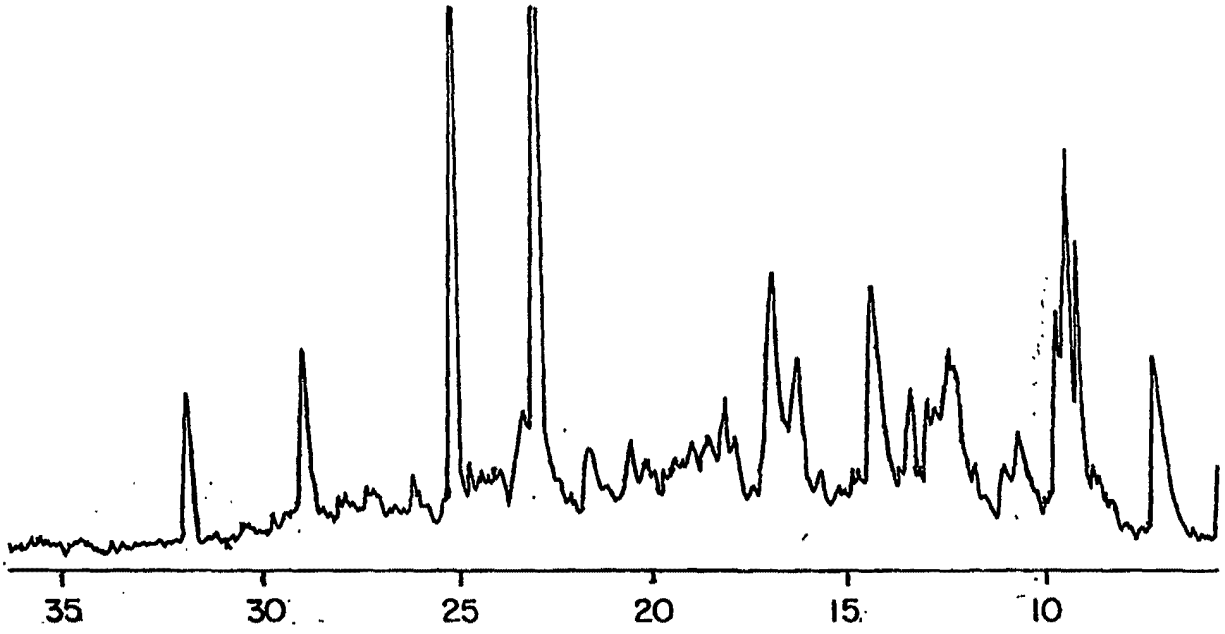


FIG. 9A

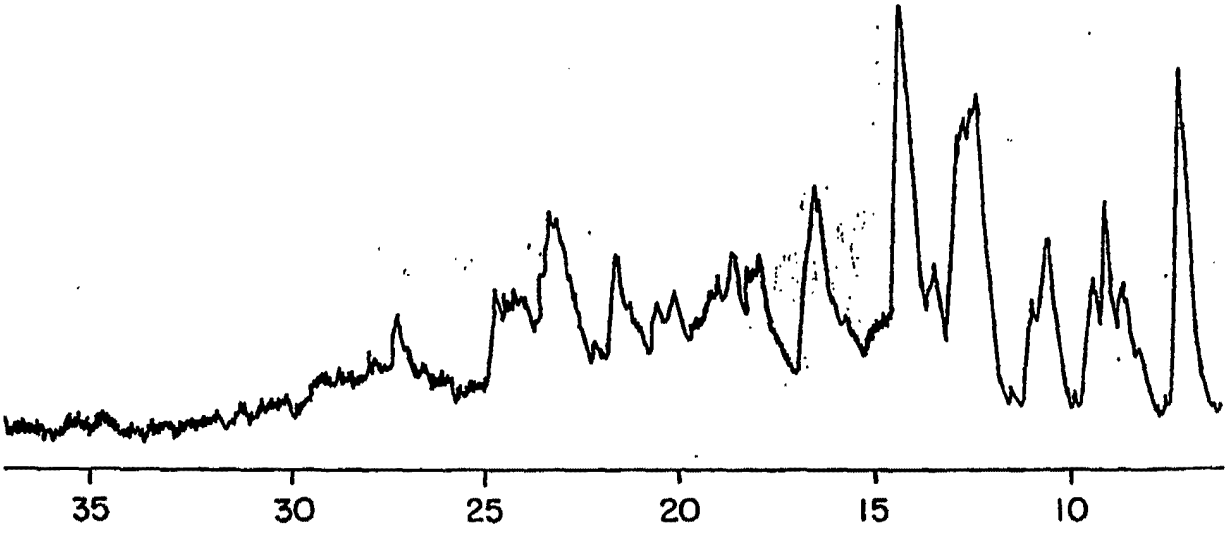


FIG. 9B

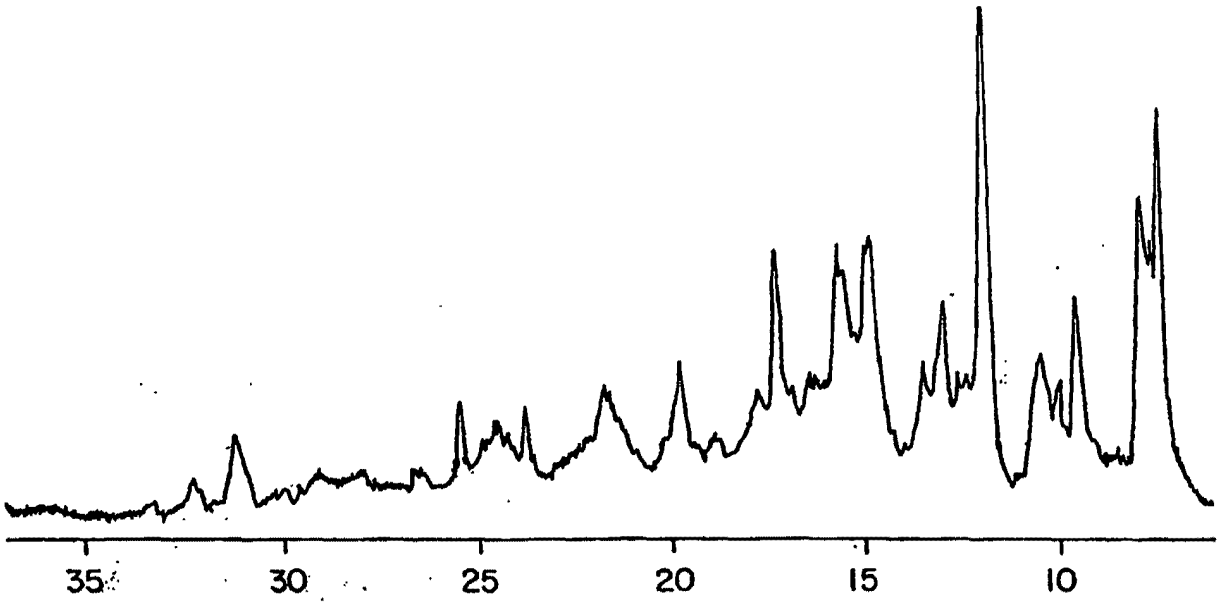


FIG. 10A

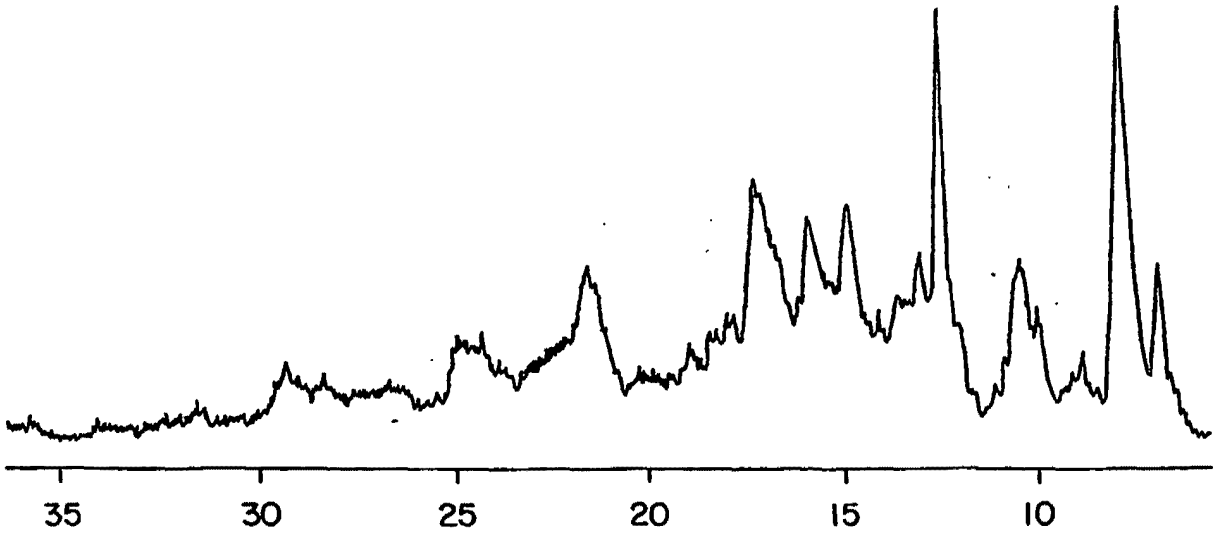


FIG. 10B

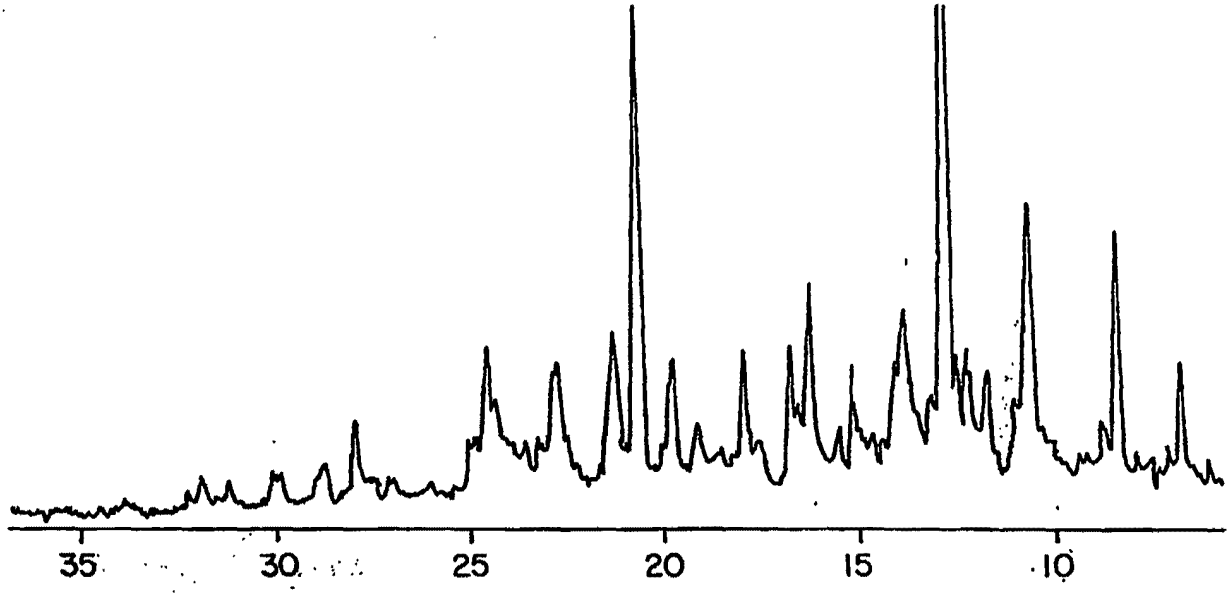


FIG. 11A

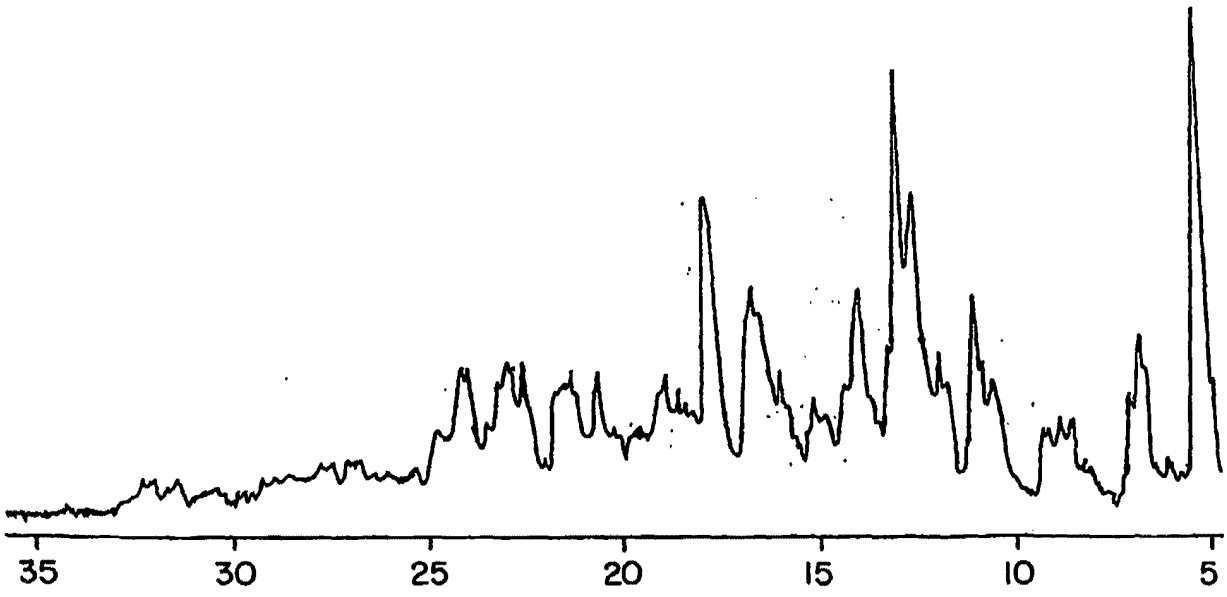


FIG. 11B

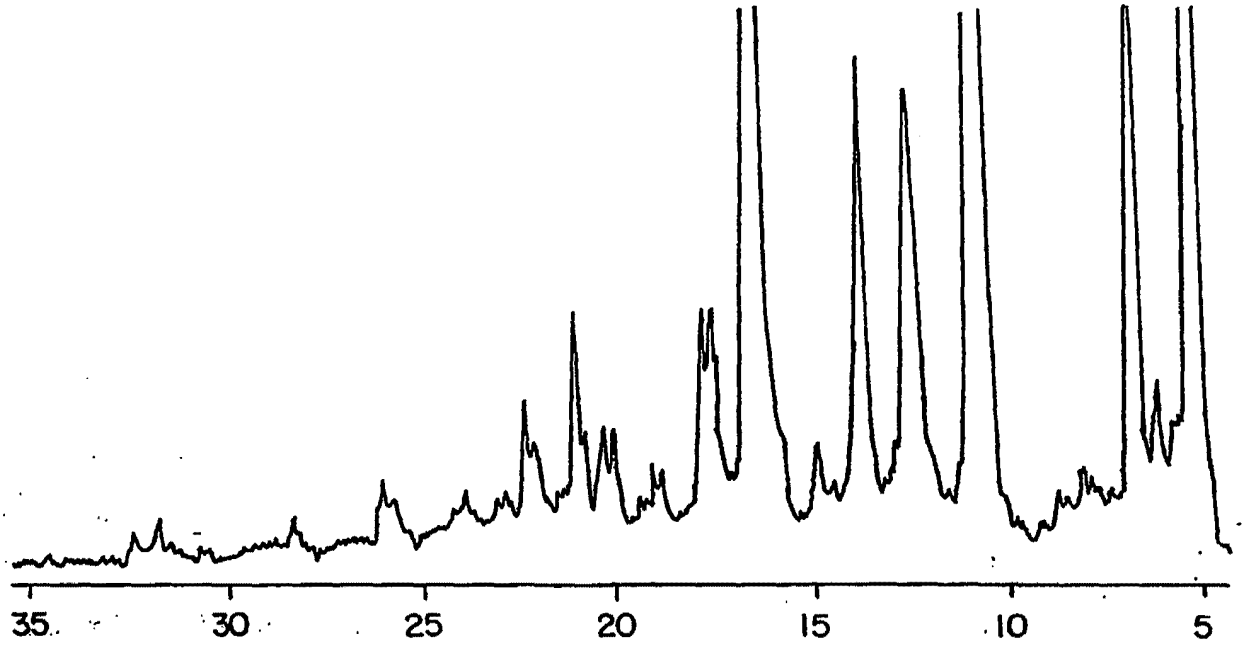


FIG. 12A

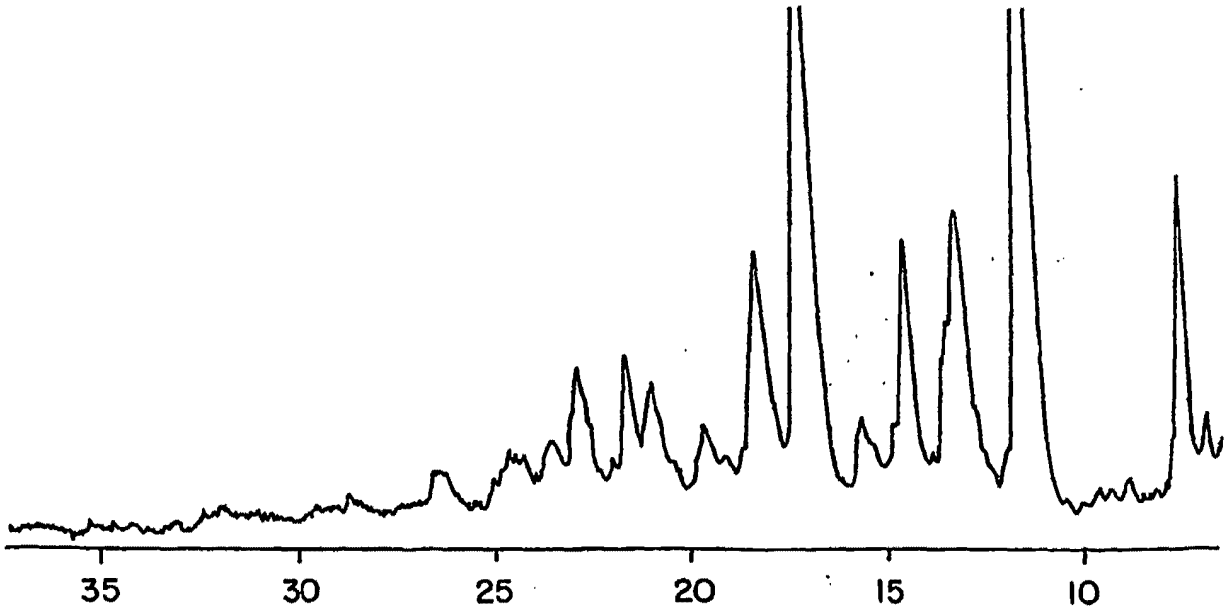


FIG. 12B

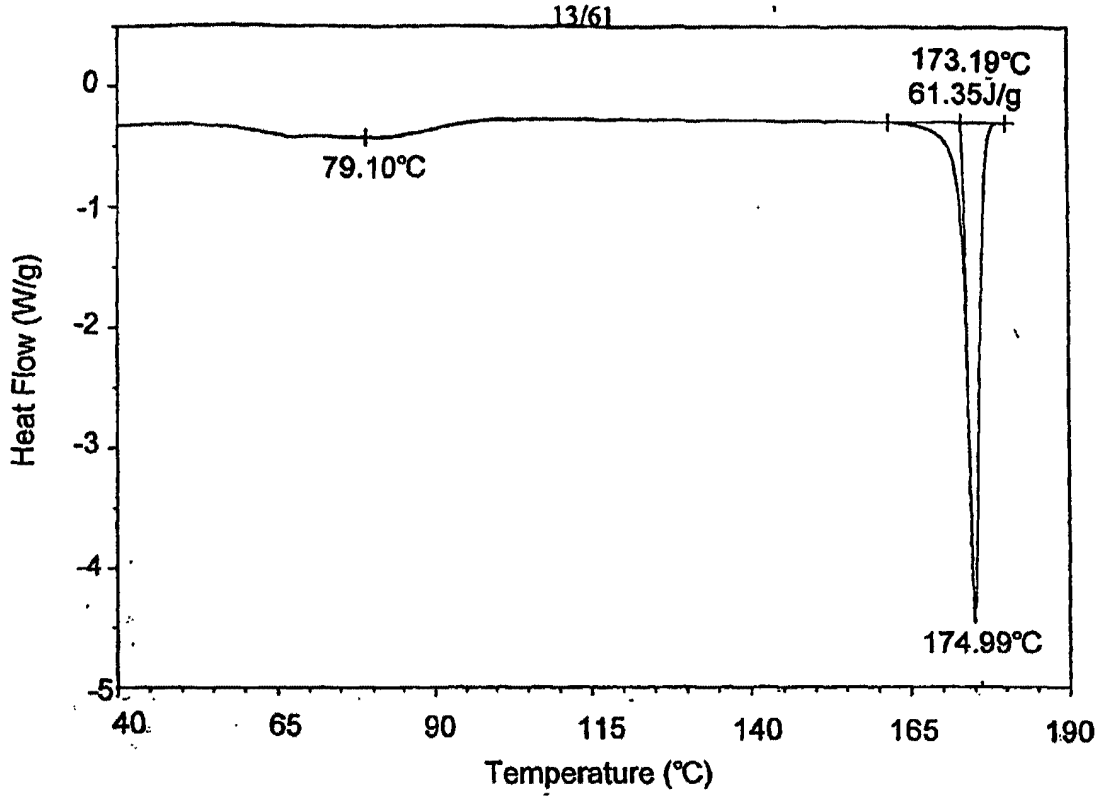


FIG. 13A

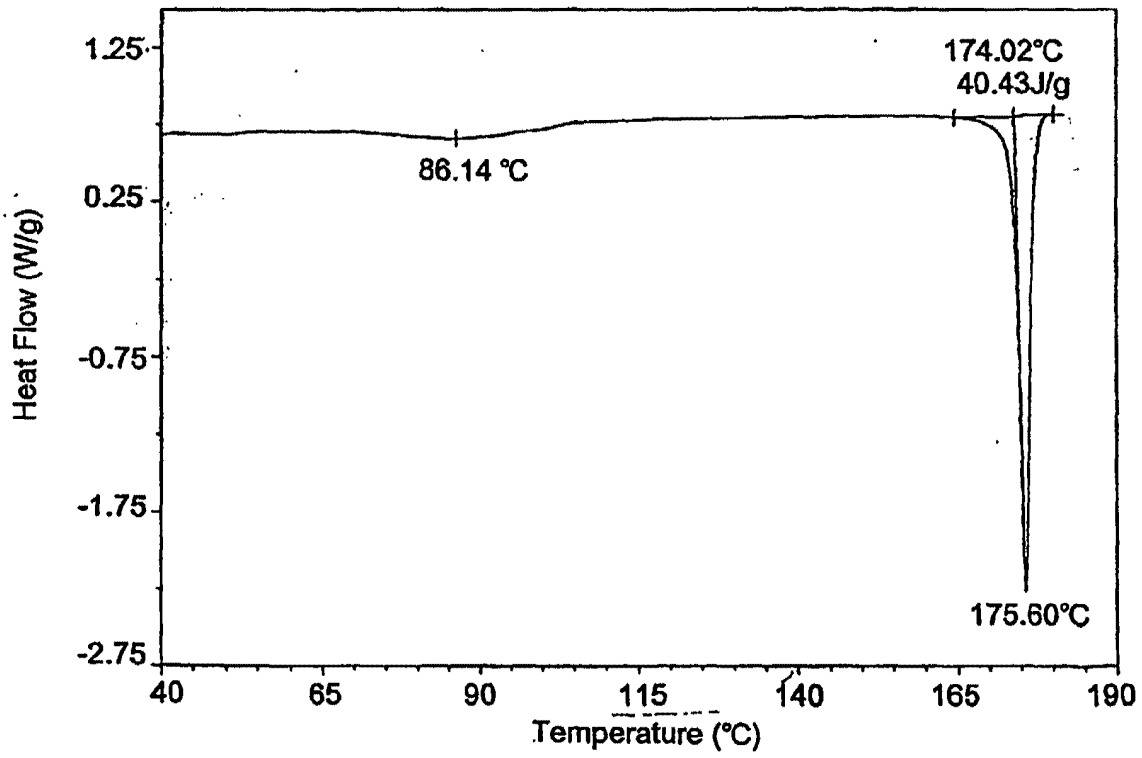


FIG. 13B

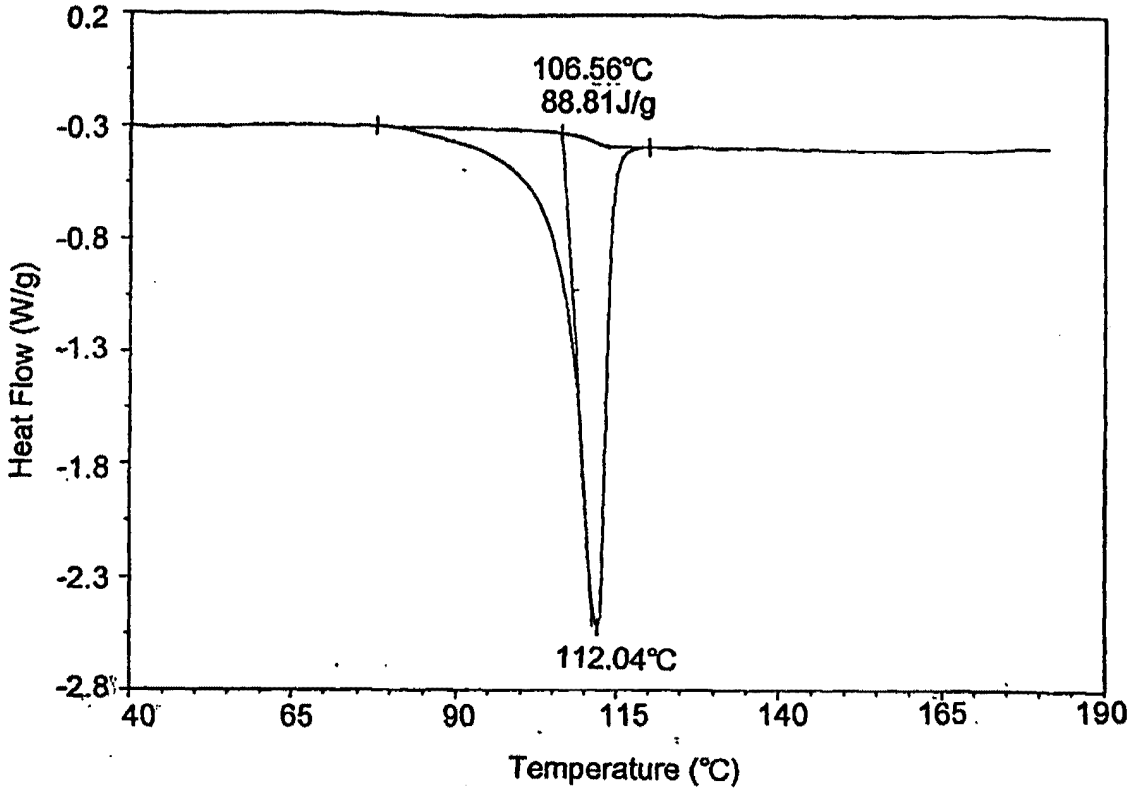


FIG. 14A

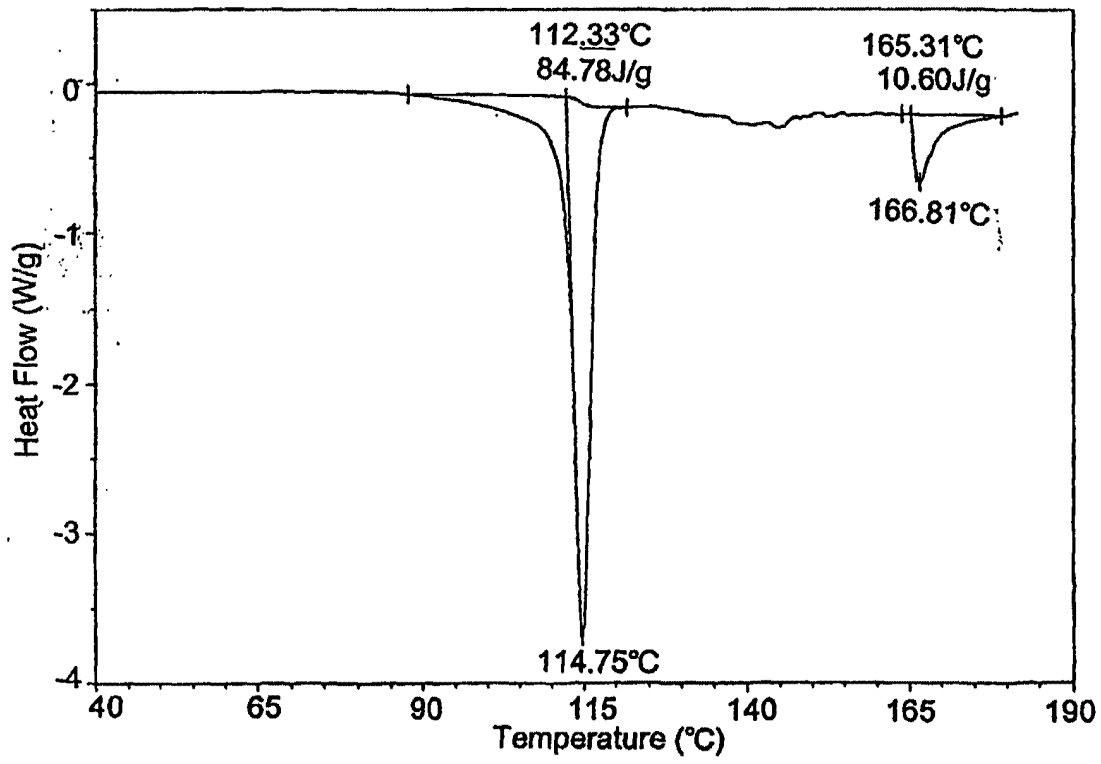


FIG. 14B

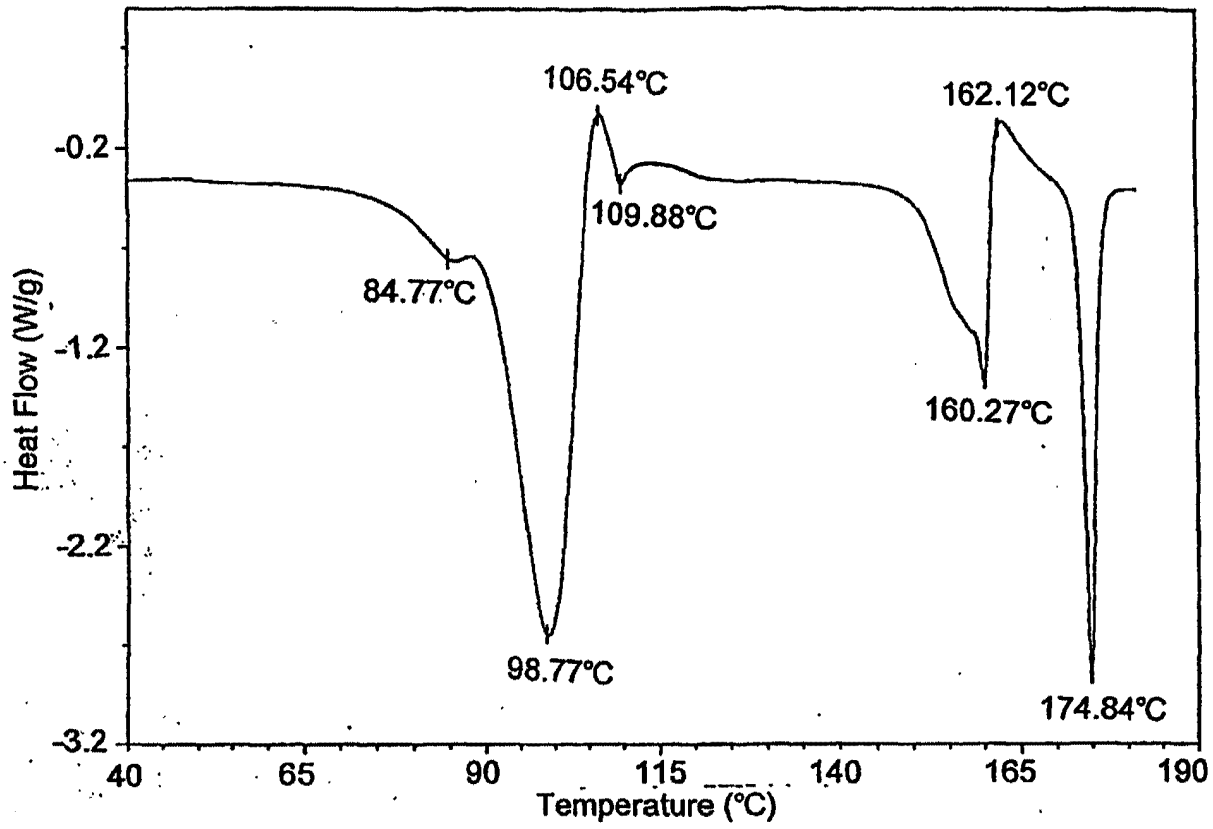

106.54°C
162.12°C
109.88°C
84.77°C
160.27°C
98.77°C
174.84°C
-0.2
-1.2
-2.2
-3.2
Heat Flow (W/g)
40
65
90
115
140
165
190
Temperature (°C)

FIG. 15

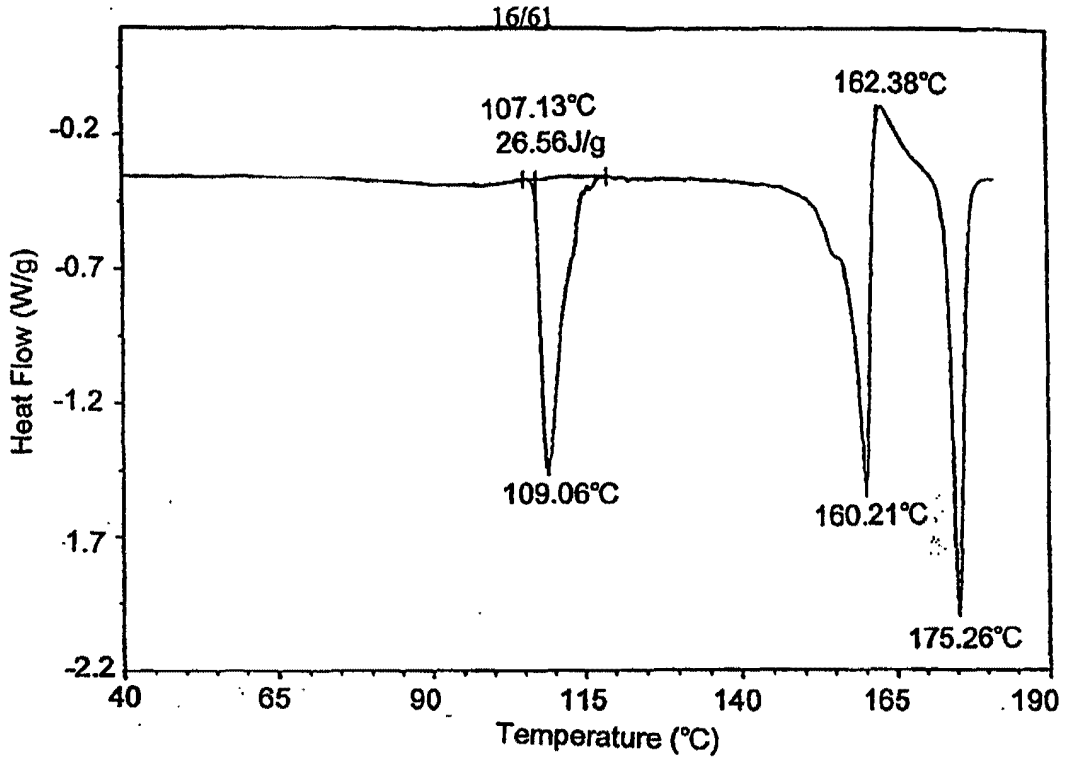


FIG. 16A

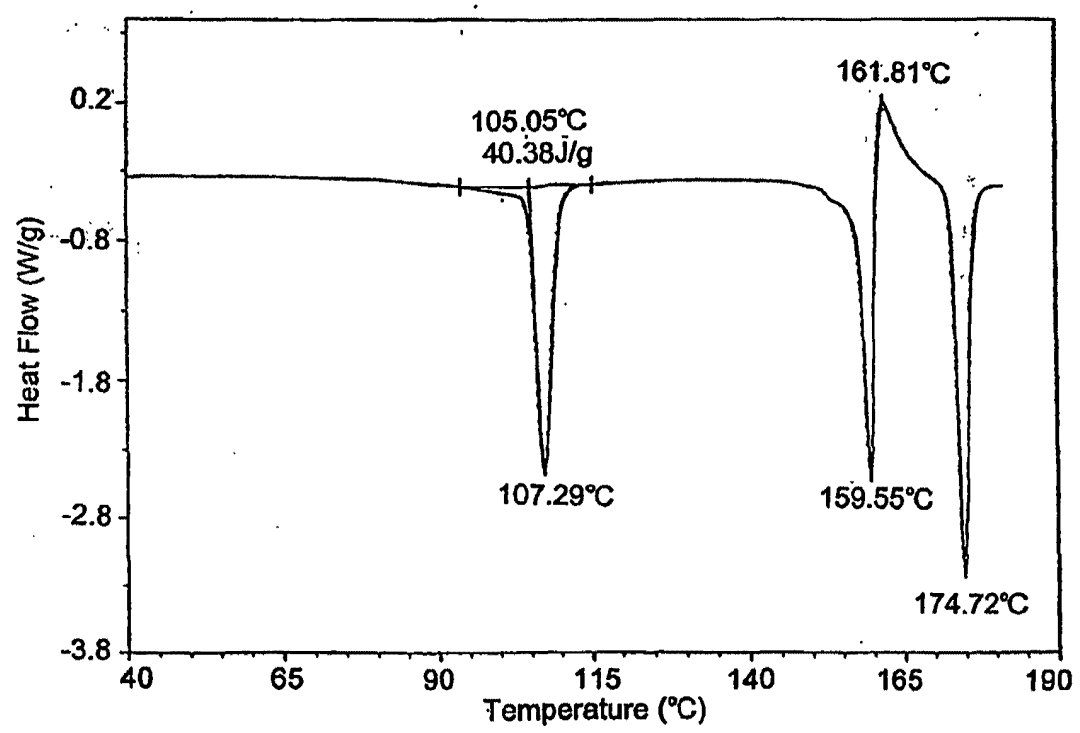


FIG. 16B

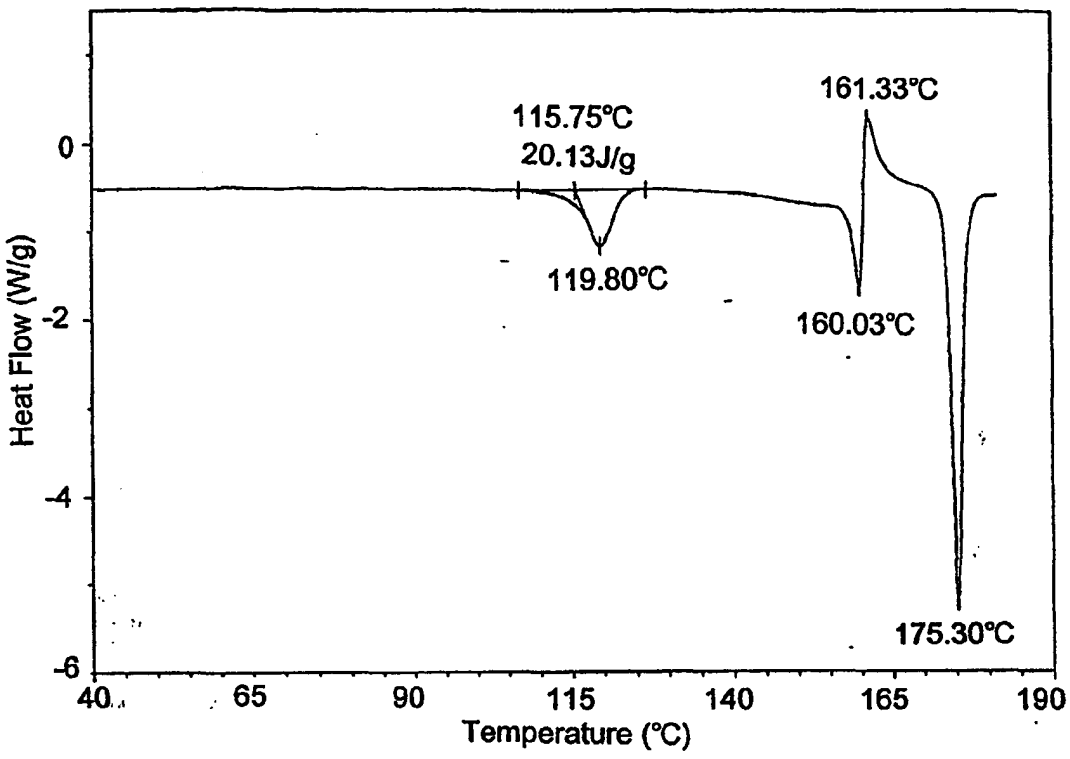


FIG. 17A

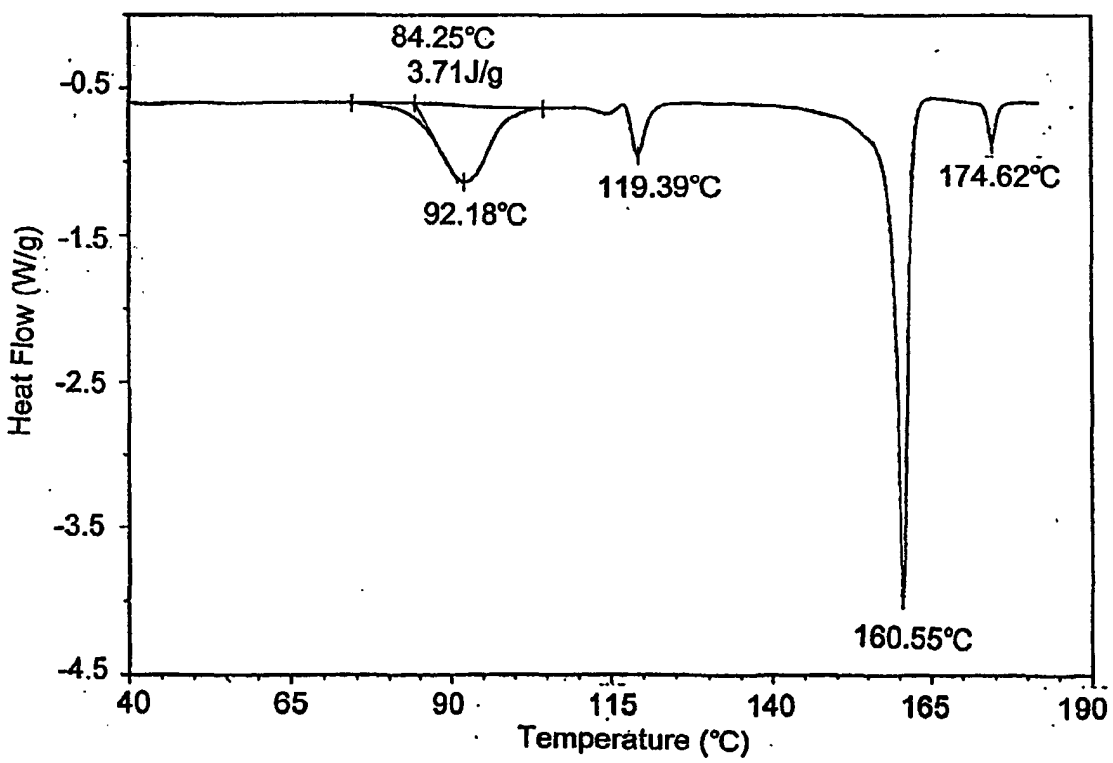


FIG. 17B

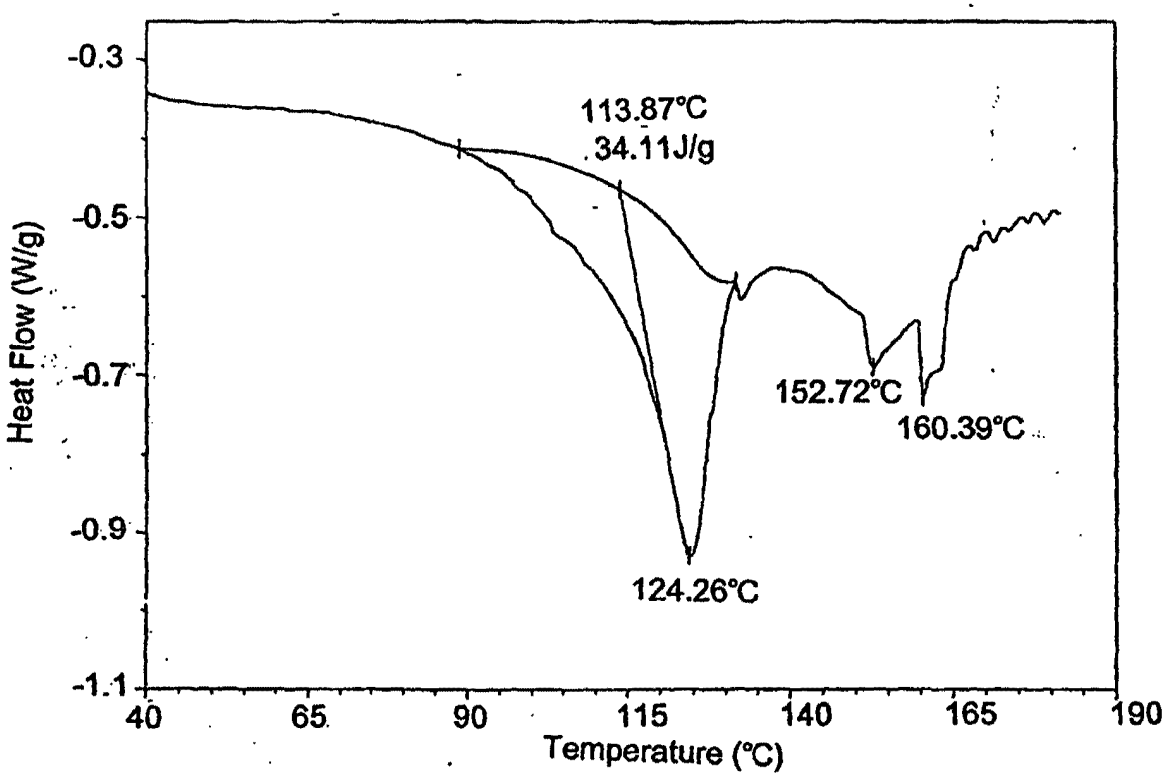

-0.3
-0.5
-0.7
-0.9
-1.1
Heat Flow (W/g)
113.87°C
34.11J/g
152.72°C
160.39°C
124.26°C
40
65
90
115
140
165
190
Temperature (°C)

FIG. 18

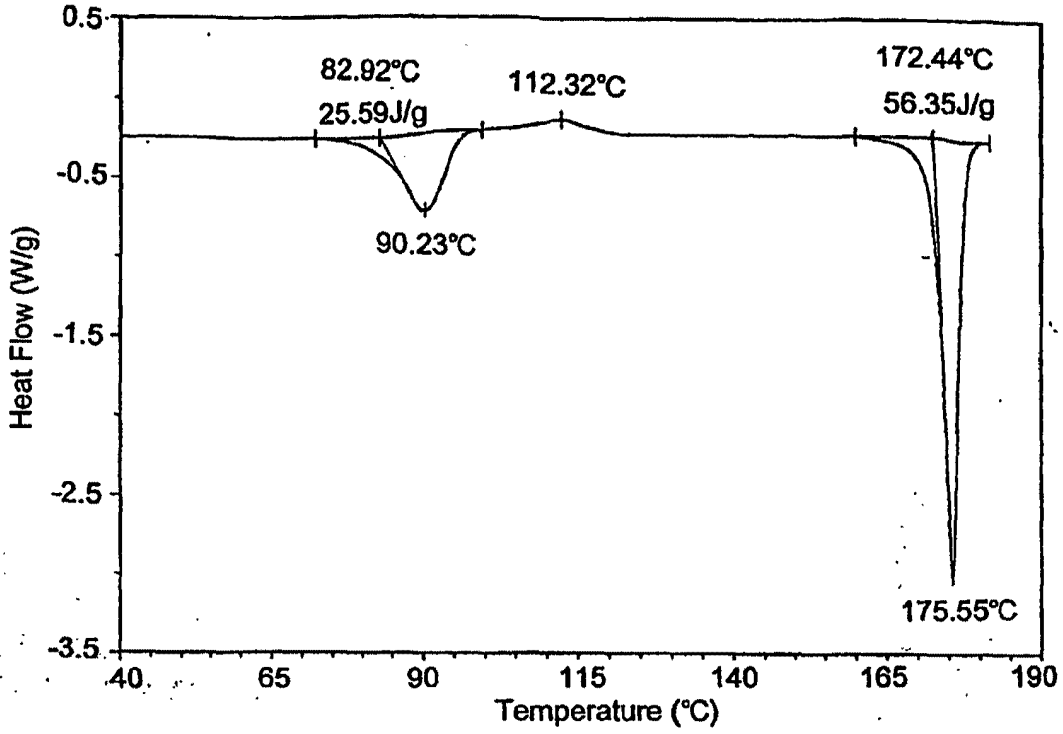


FIG. 19A

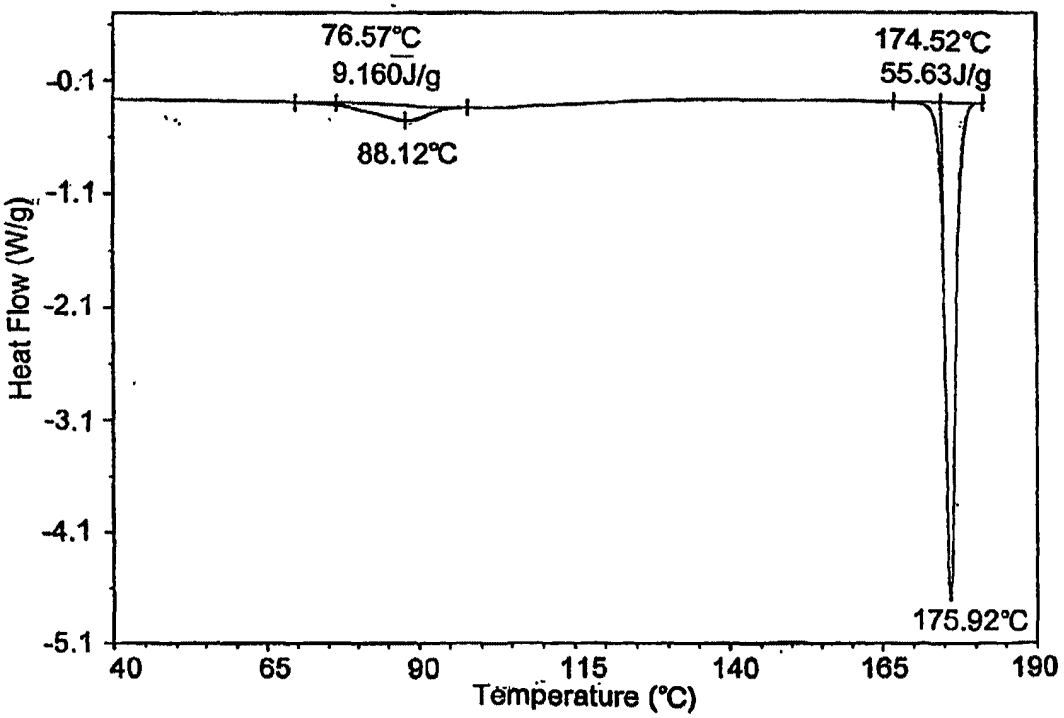


FIG. 19B

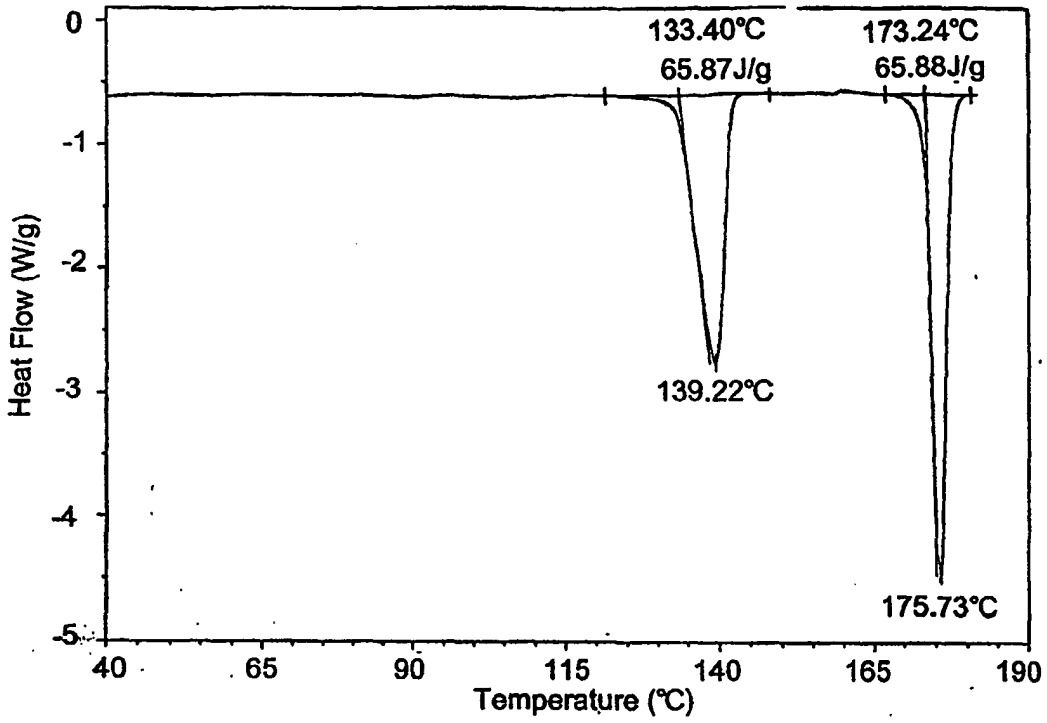


FIG. 20A

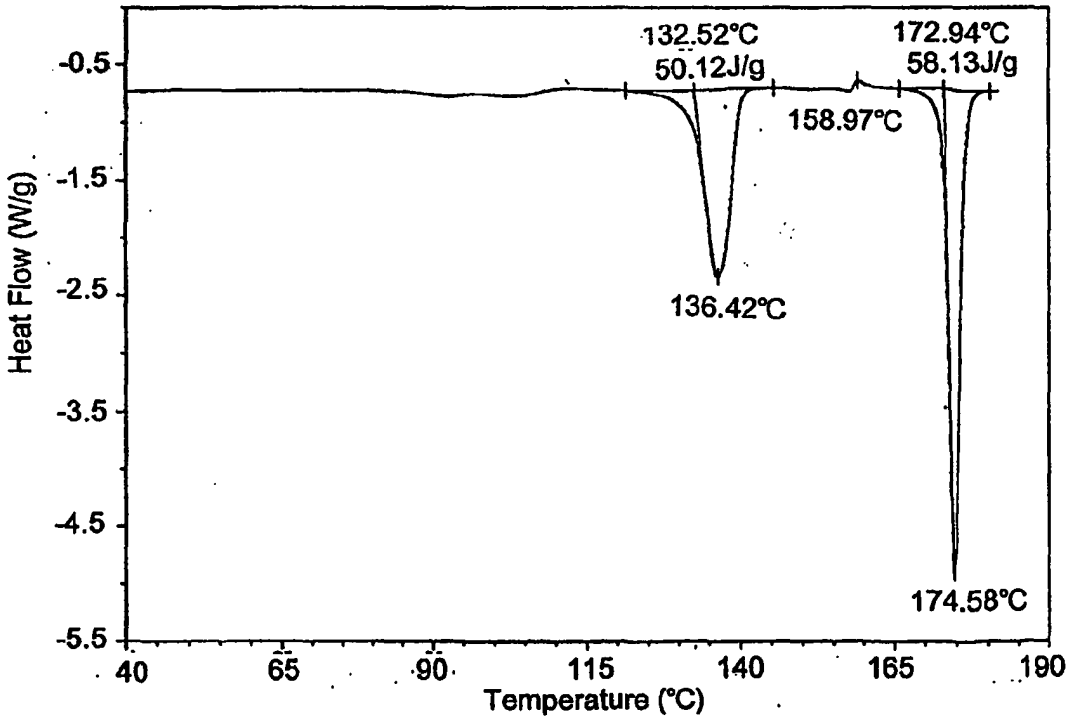


FIG. 20B

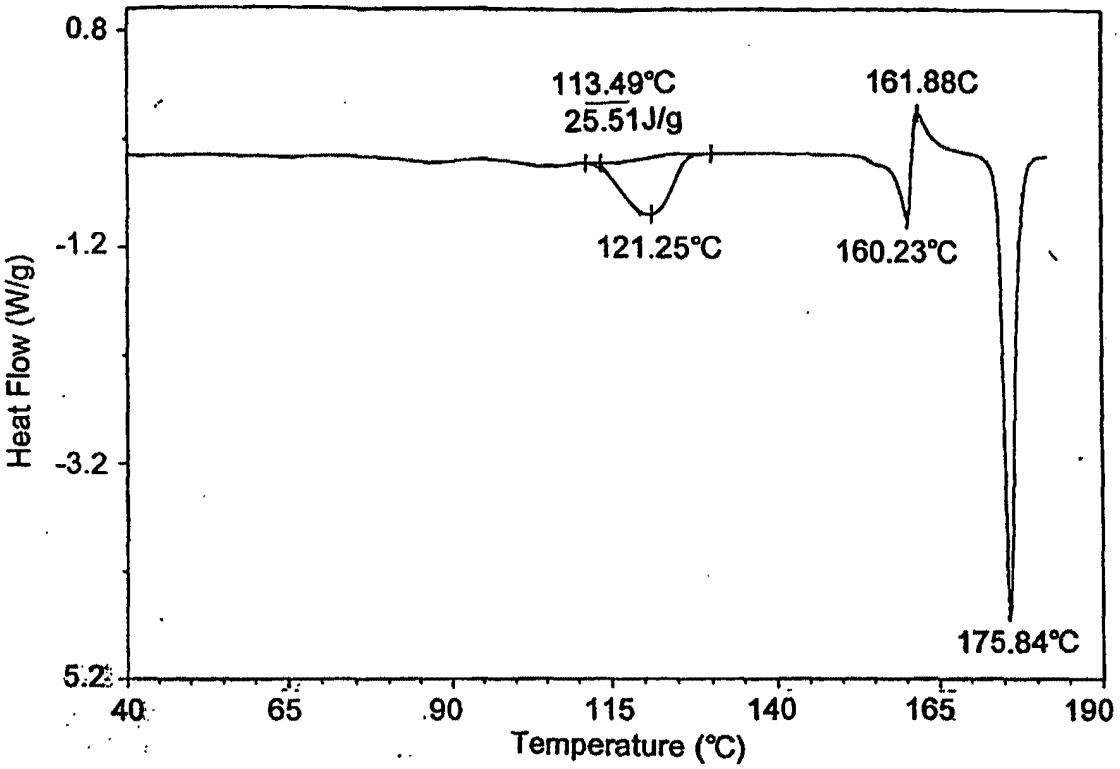


FIG. 21A

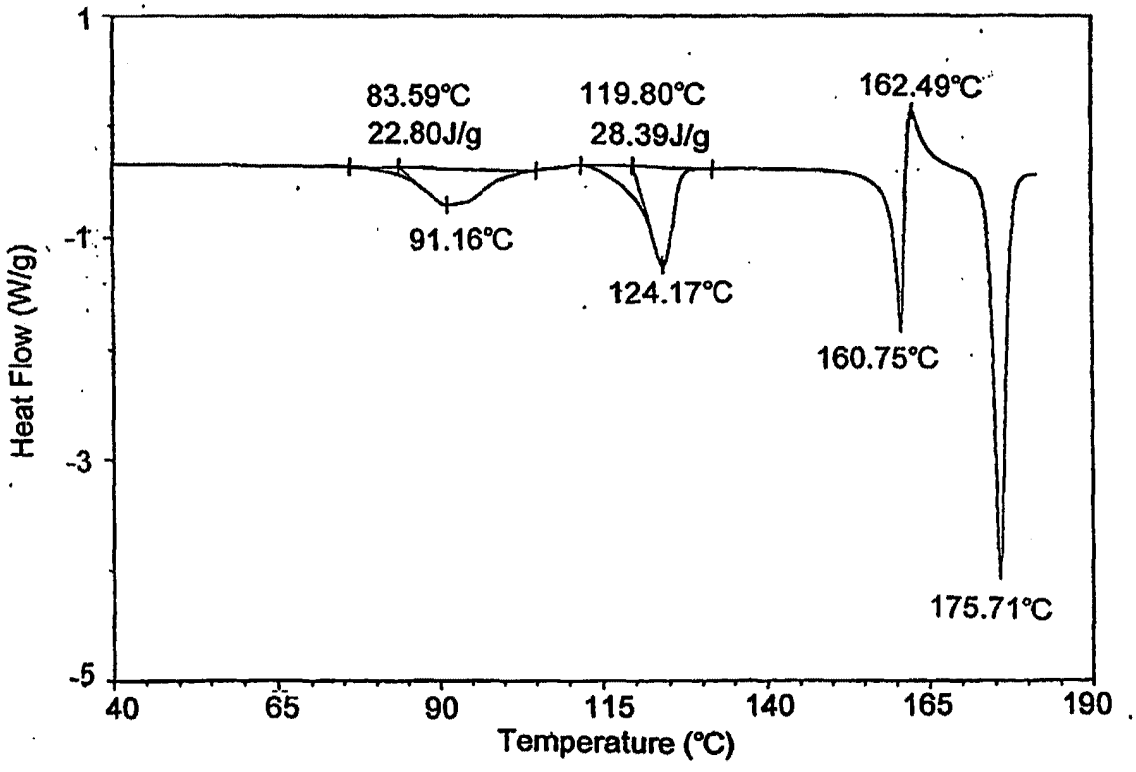


FIG. 21B

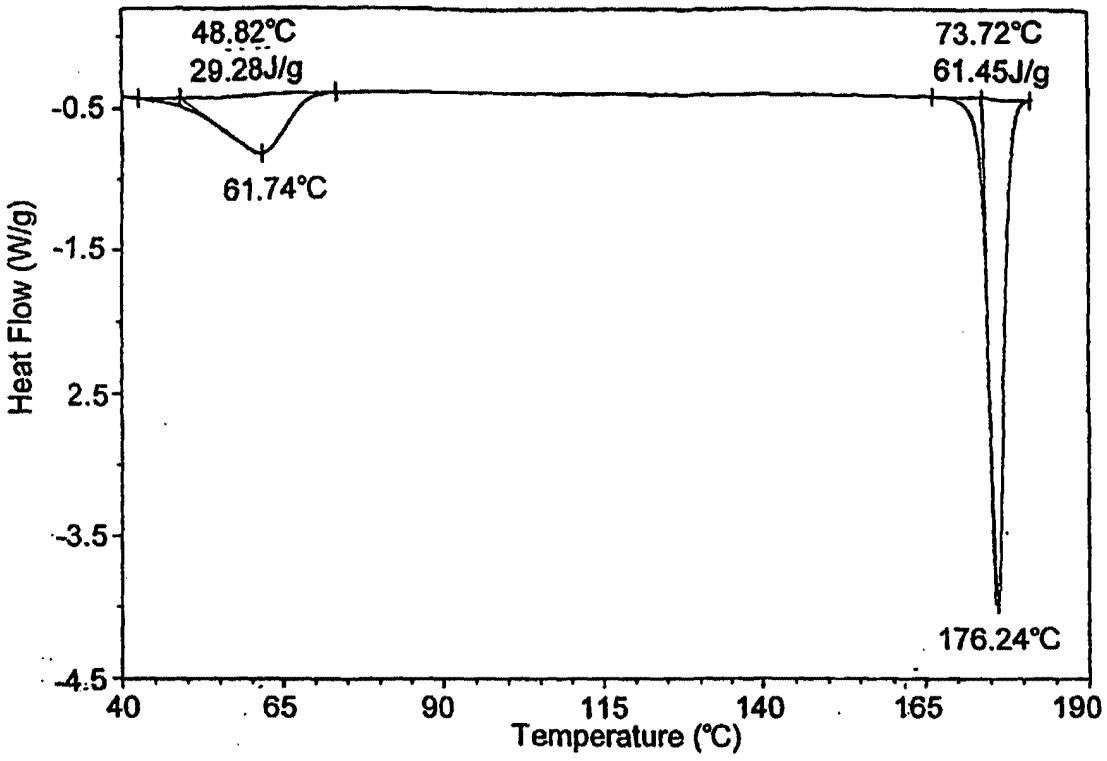


FIG. 22A

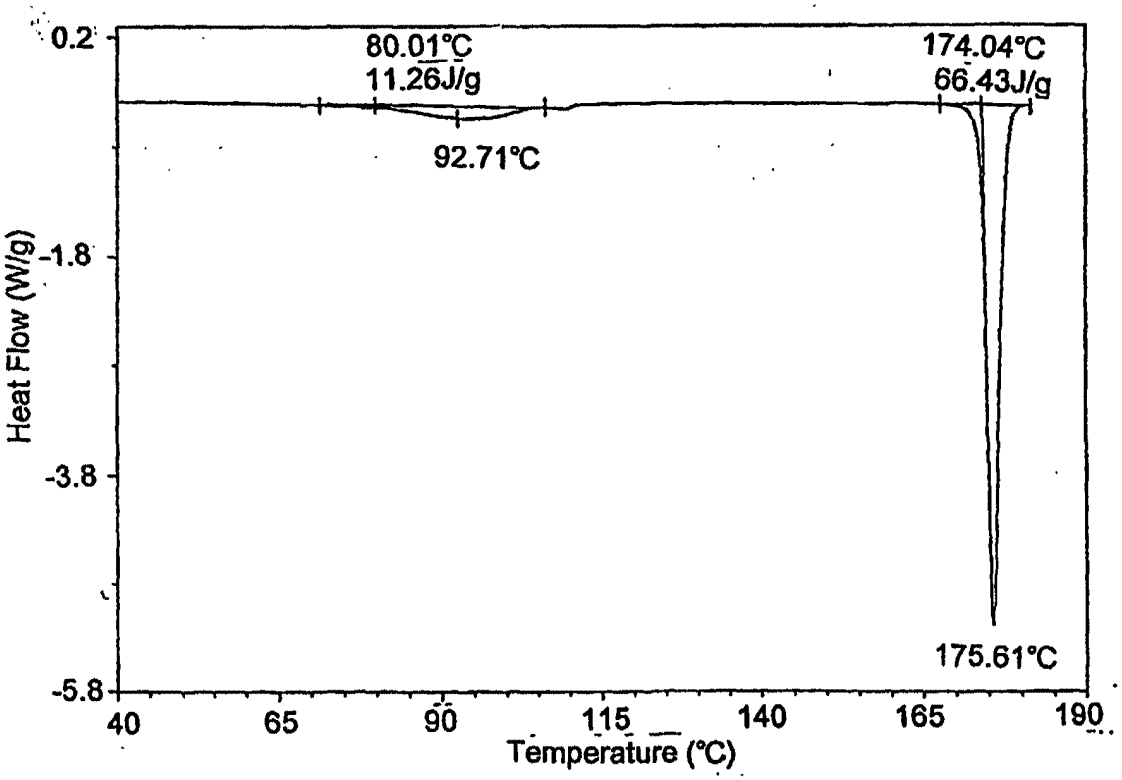


FIG. 22B

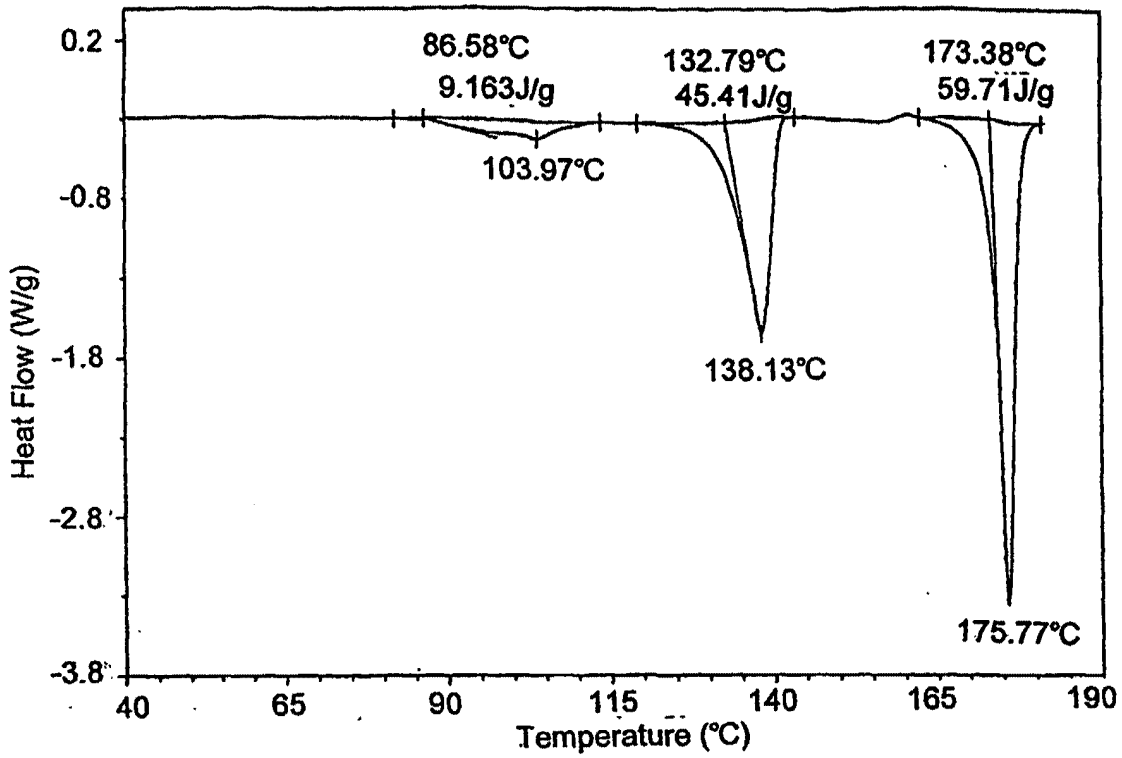


FIG. 23A

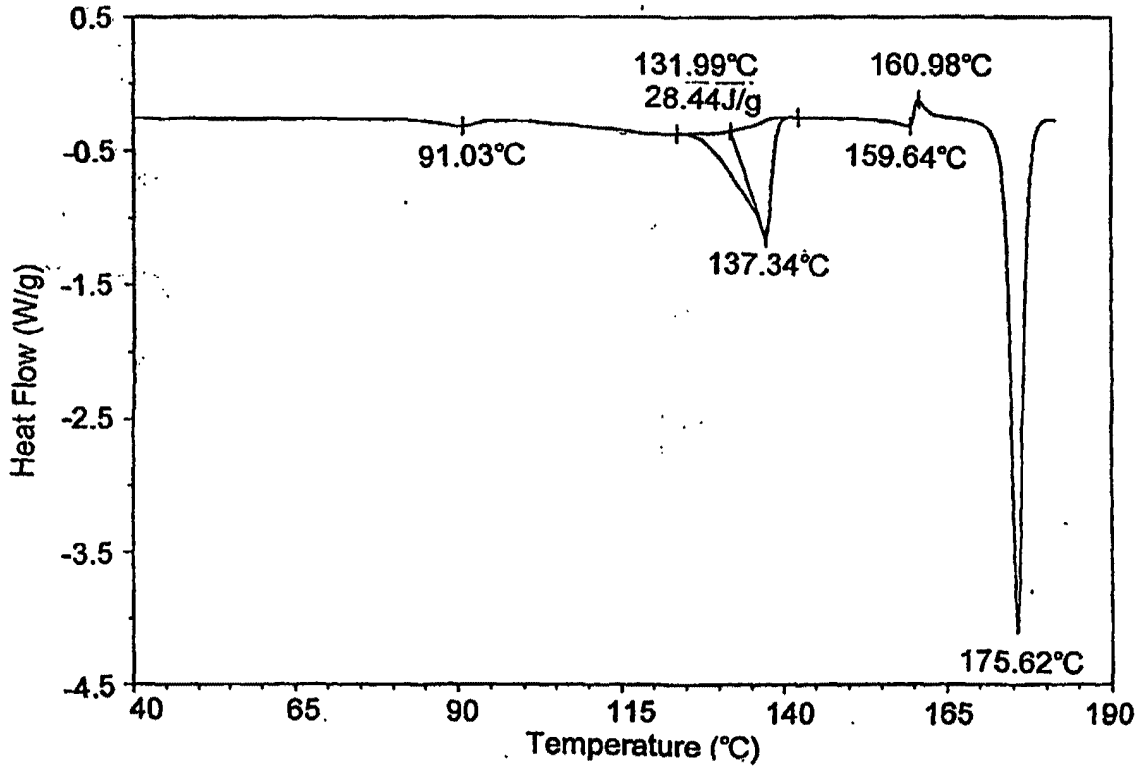


FIG. 23B

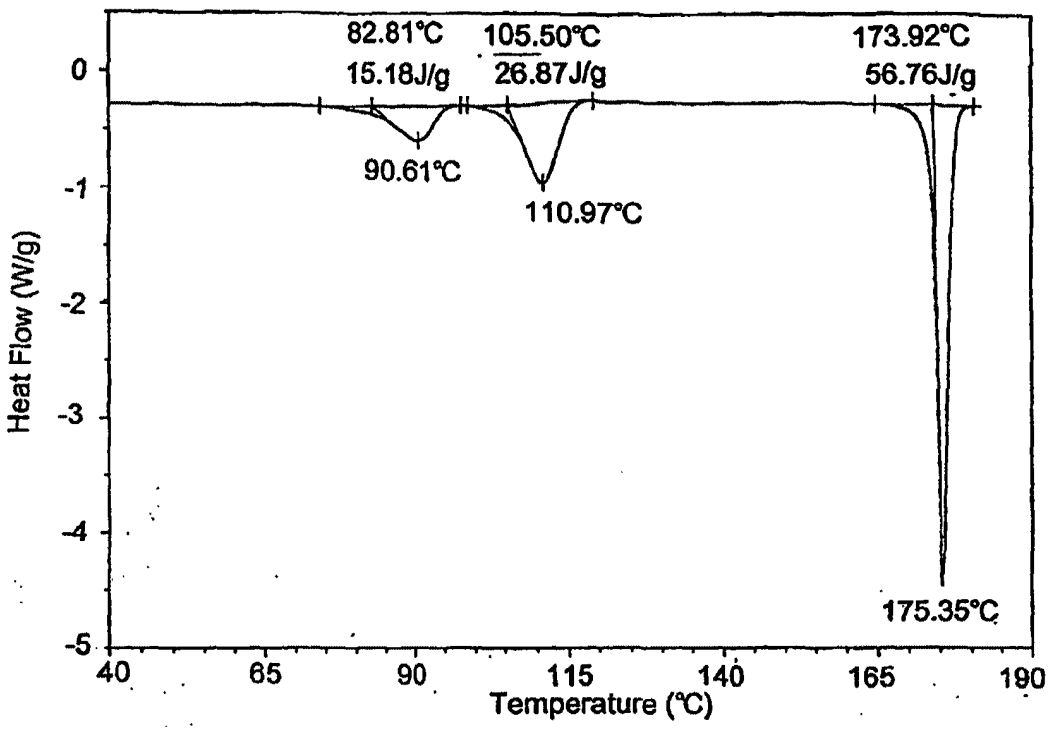


FIG. 24A

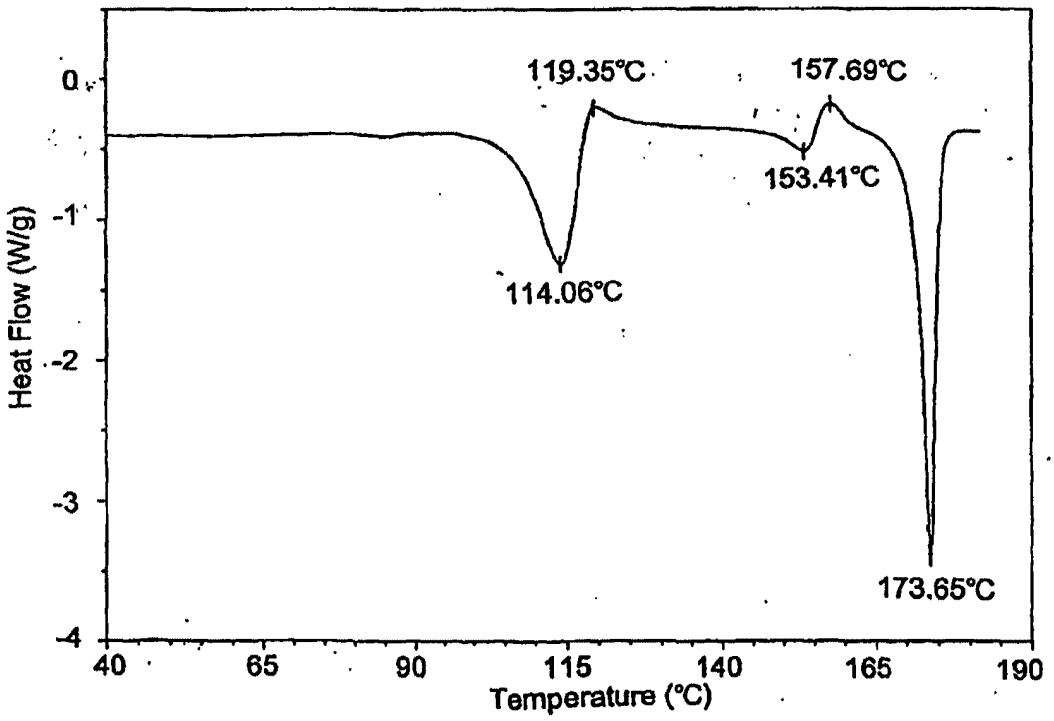


FIG. 24B

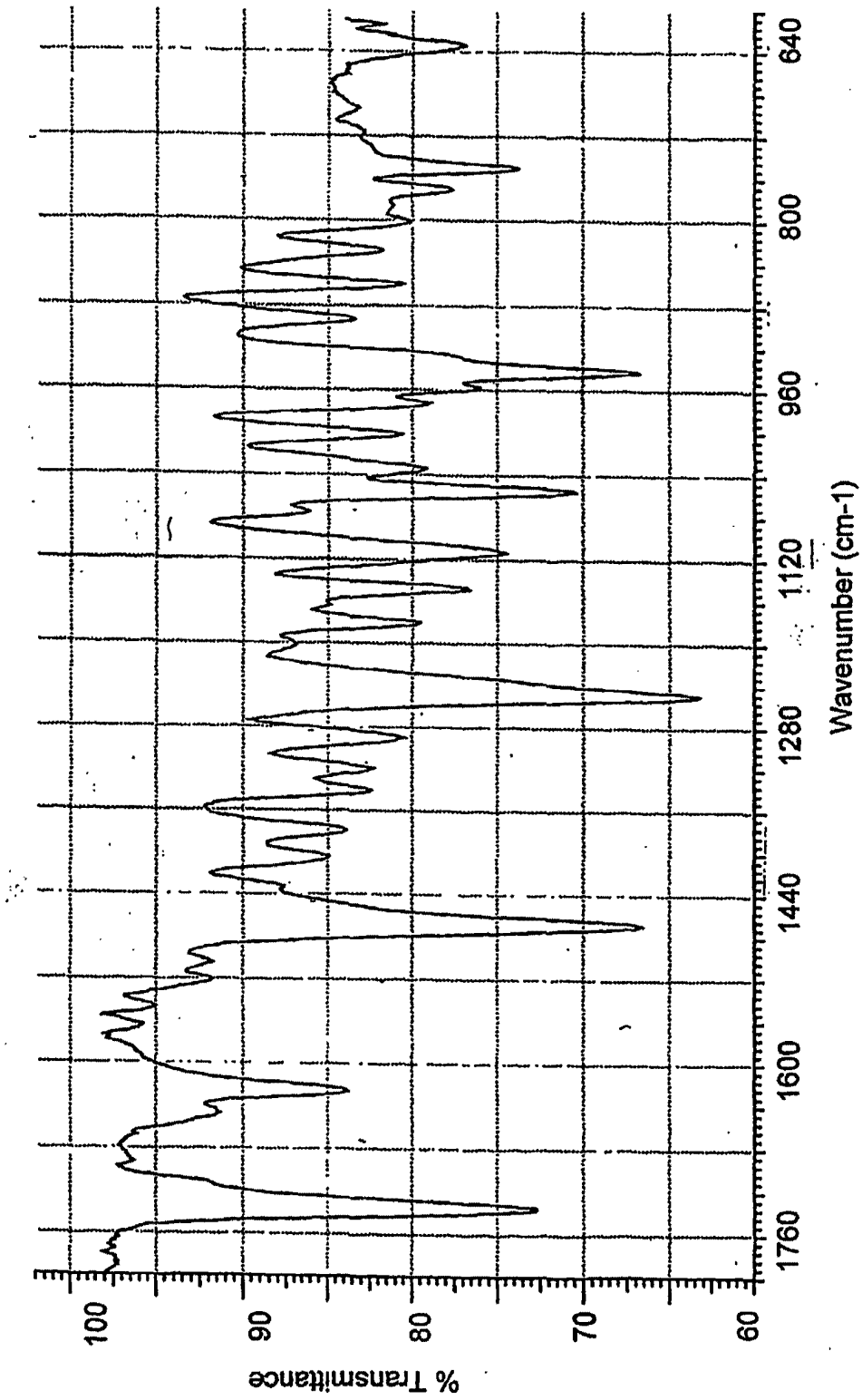

% Transmittance
100
90
80
70
60
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 25A

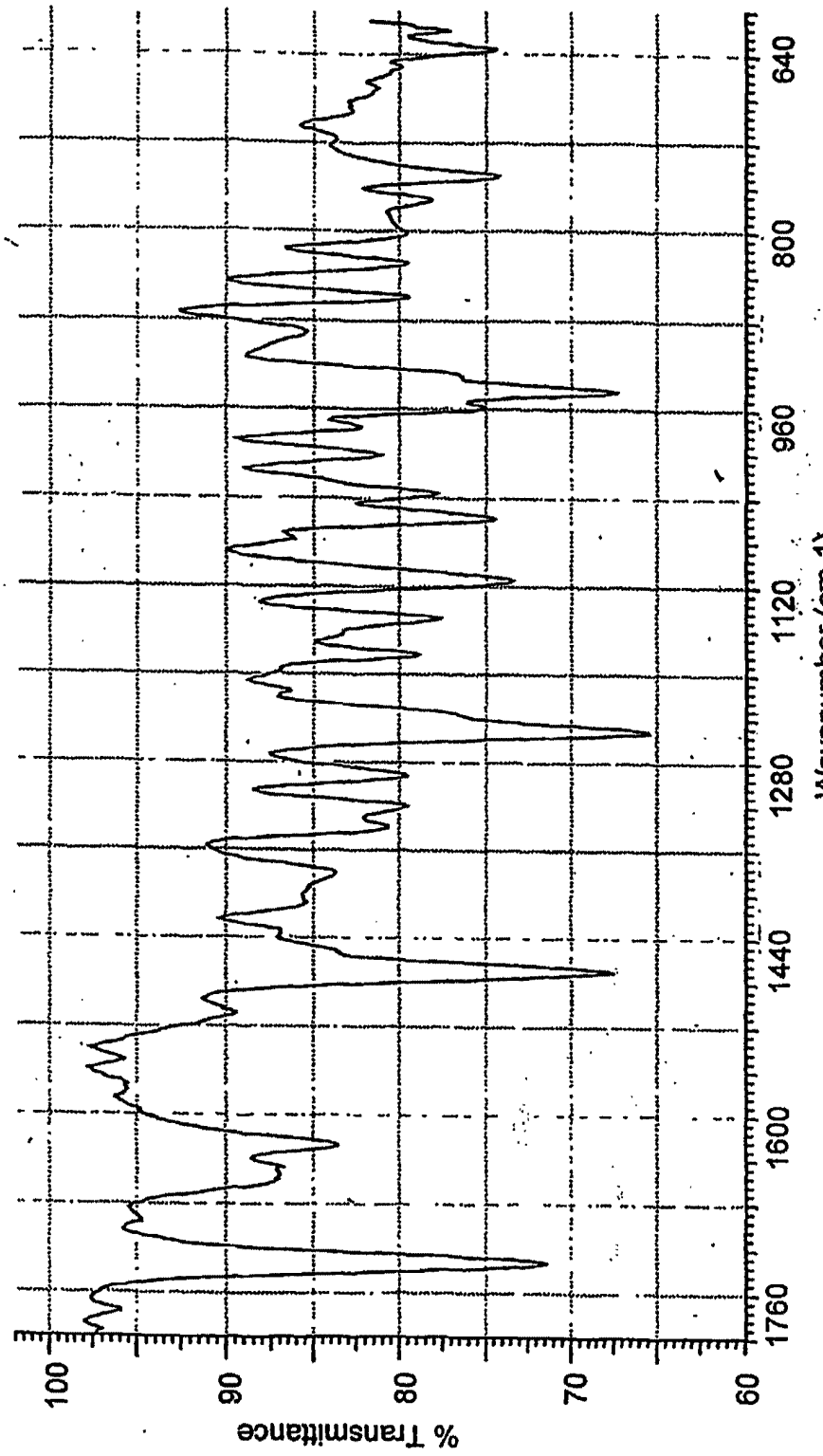

% Transmittance
100
90
80
70
60
Wavenumber (cm-1)
1760
1600
1440
1280
1120
960
800
640

FIG. 25B

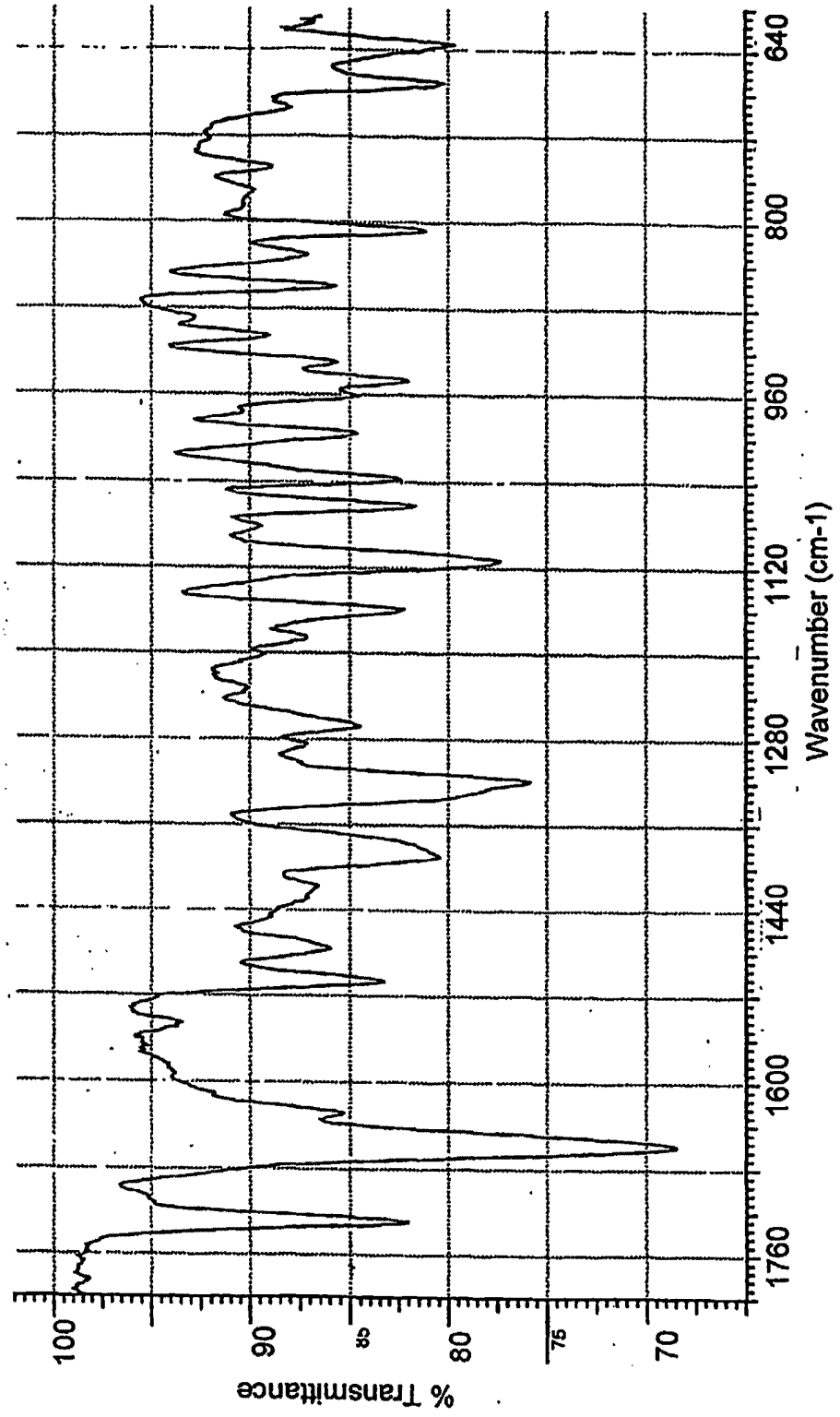

% Transmittance
100
90
85
80
75
70
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 26A

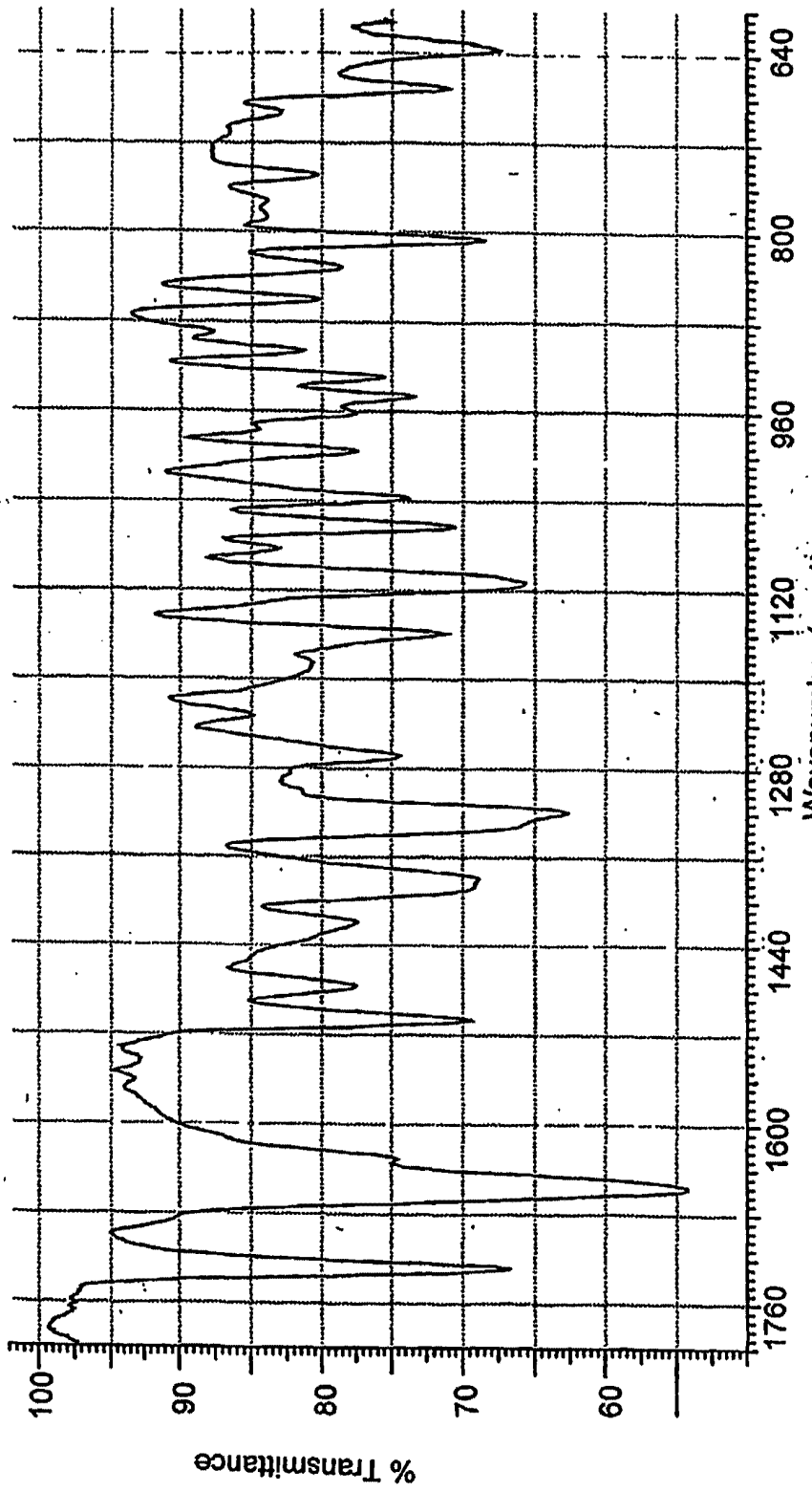

% Transmittance
100
90
80
70
60
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 26B

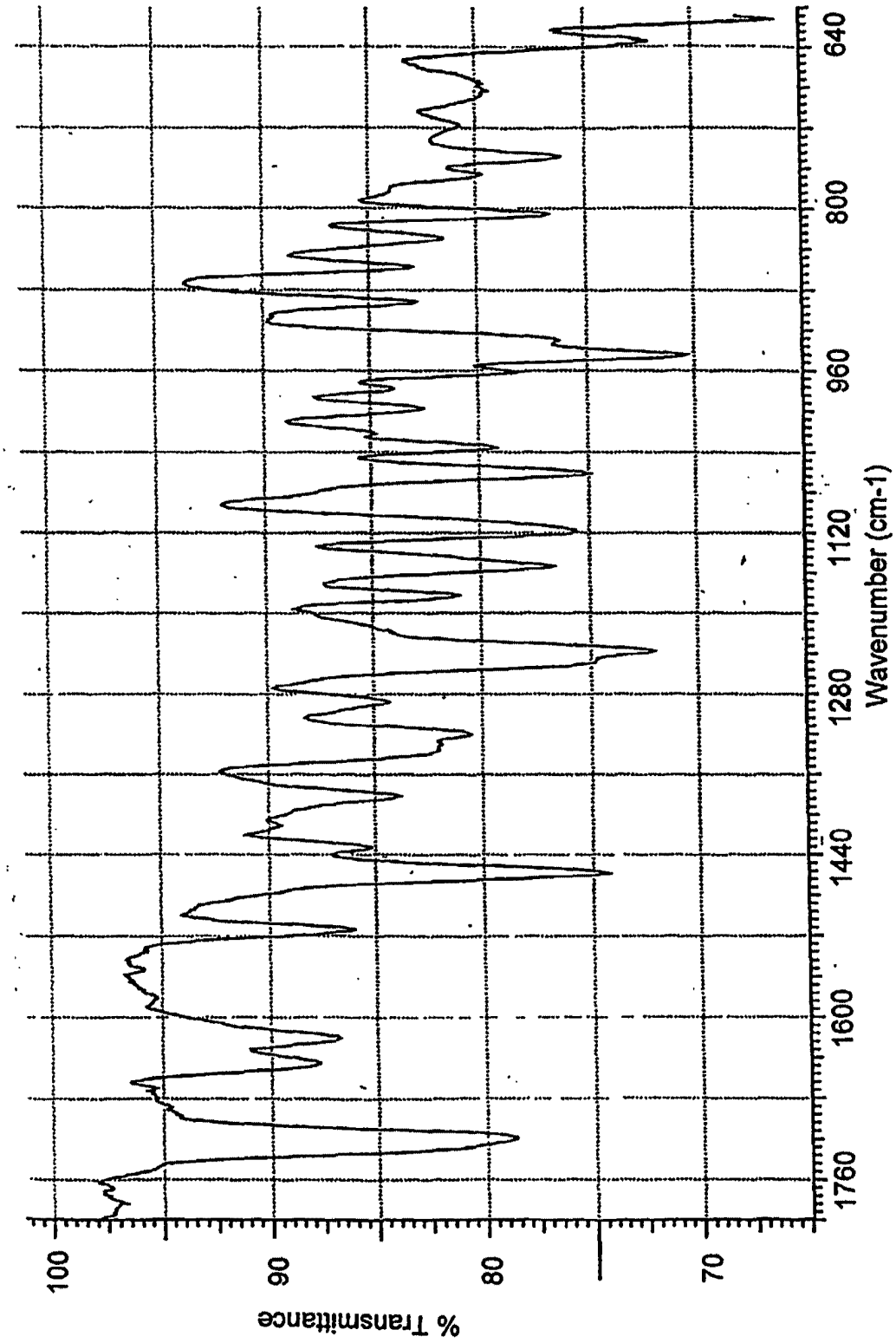

% Transmittance
100
90
80
70
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 27

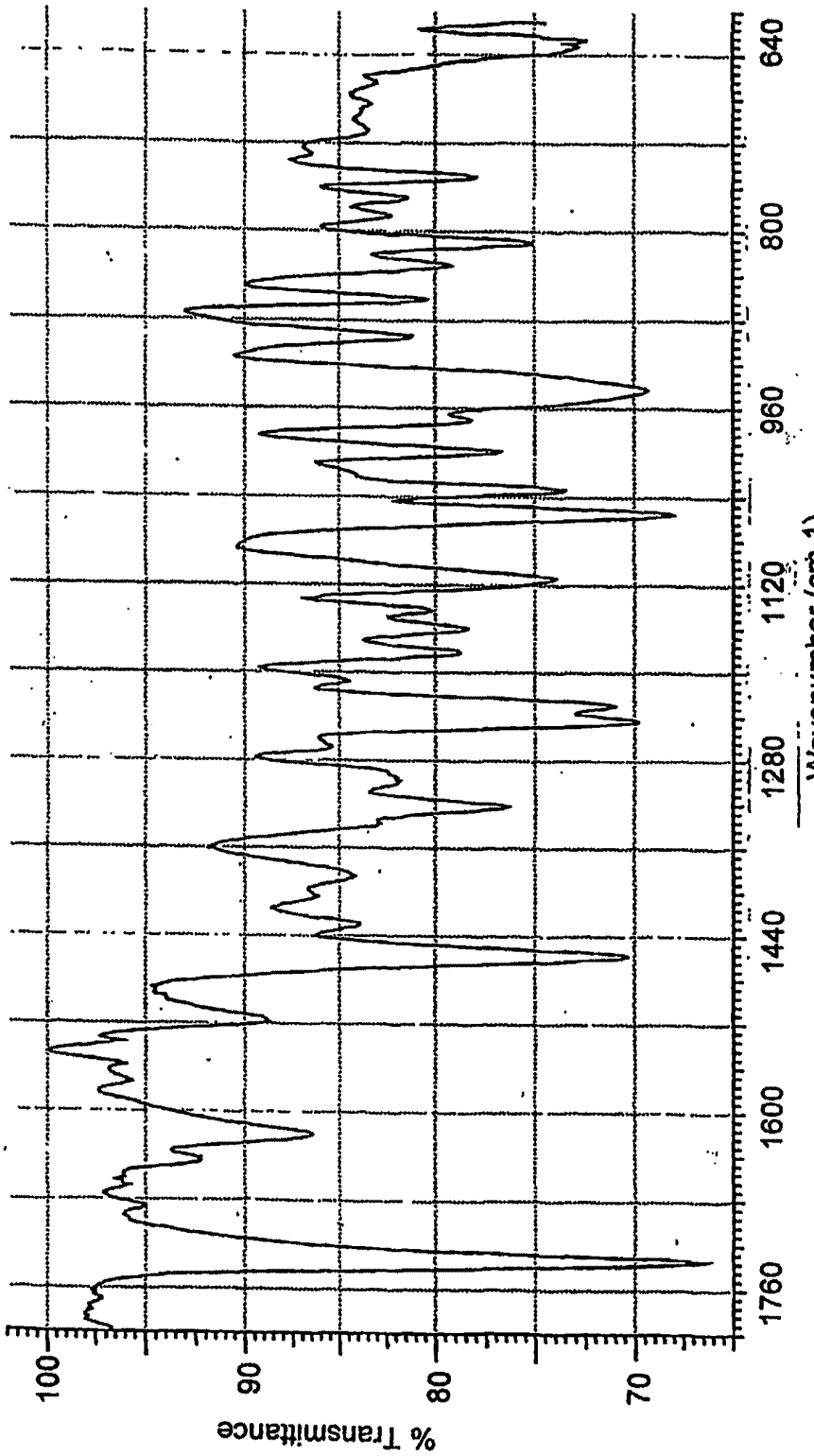

% Transmittance
100
90
80
70
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 28A

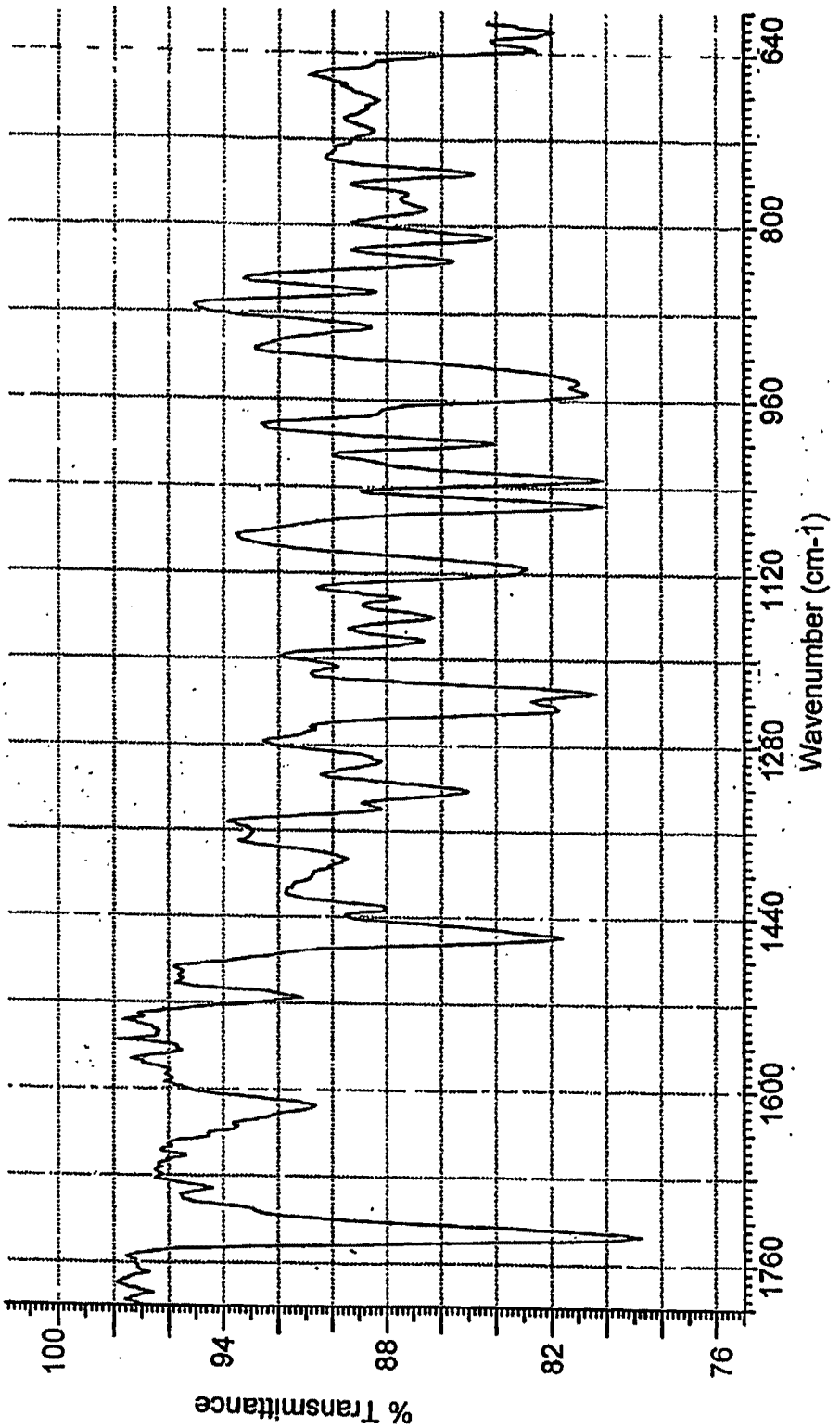

% Transmittance
100
94
88
82
76
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 28B

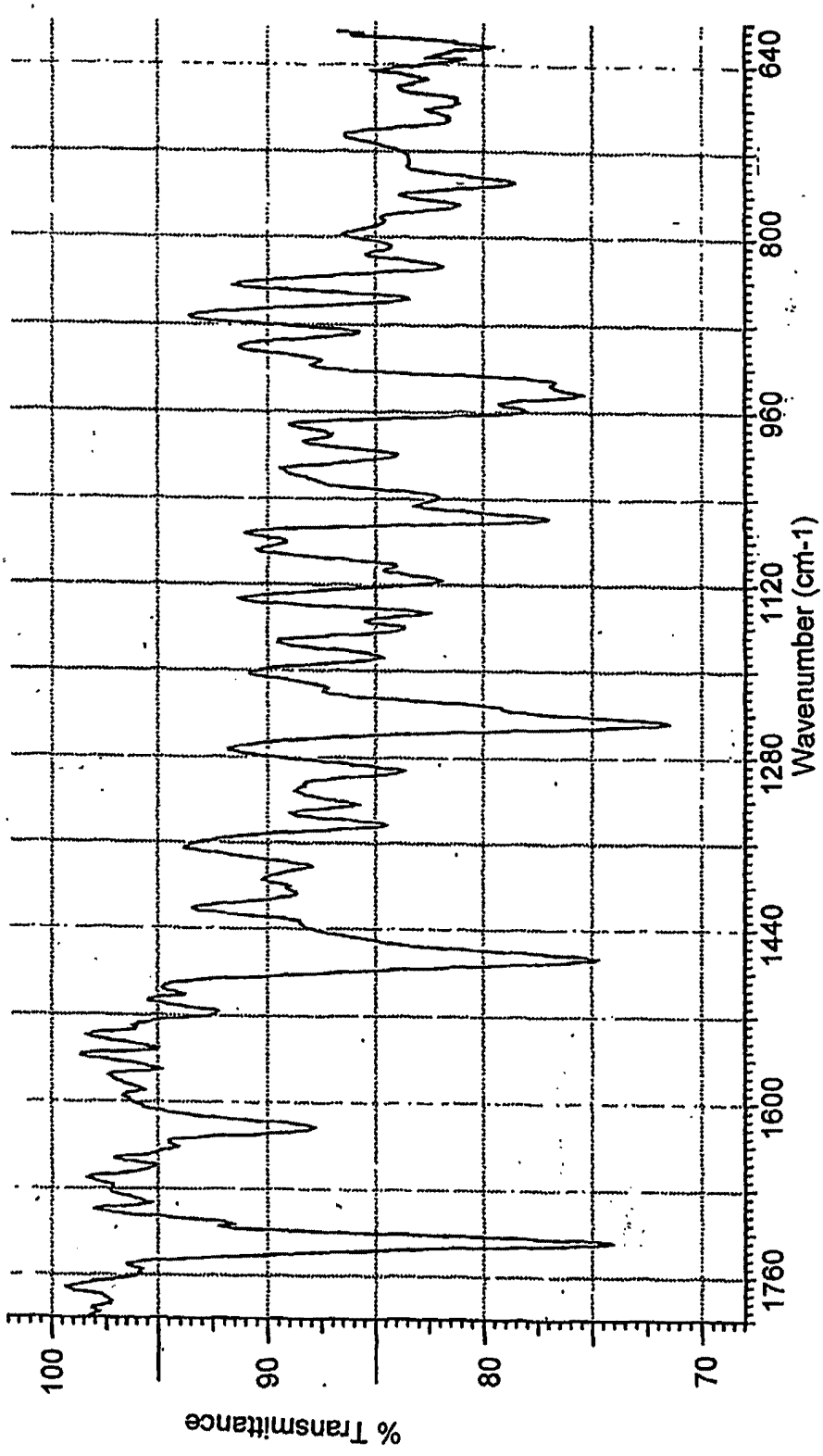

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 29A

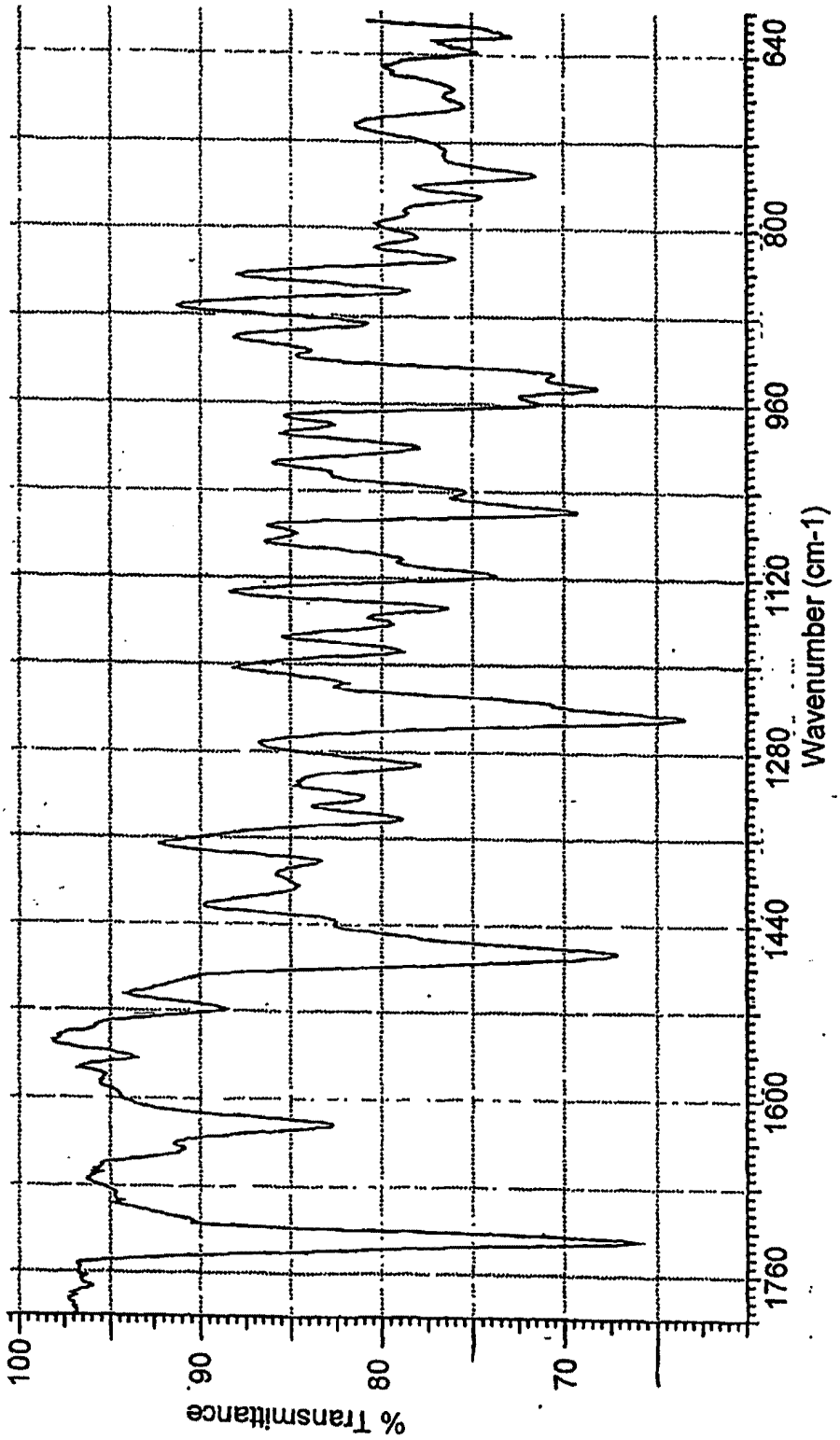

100
90
80
70
% Transmittance
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 29B

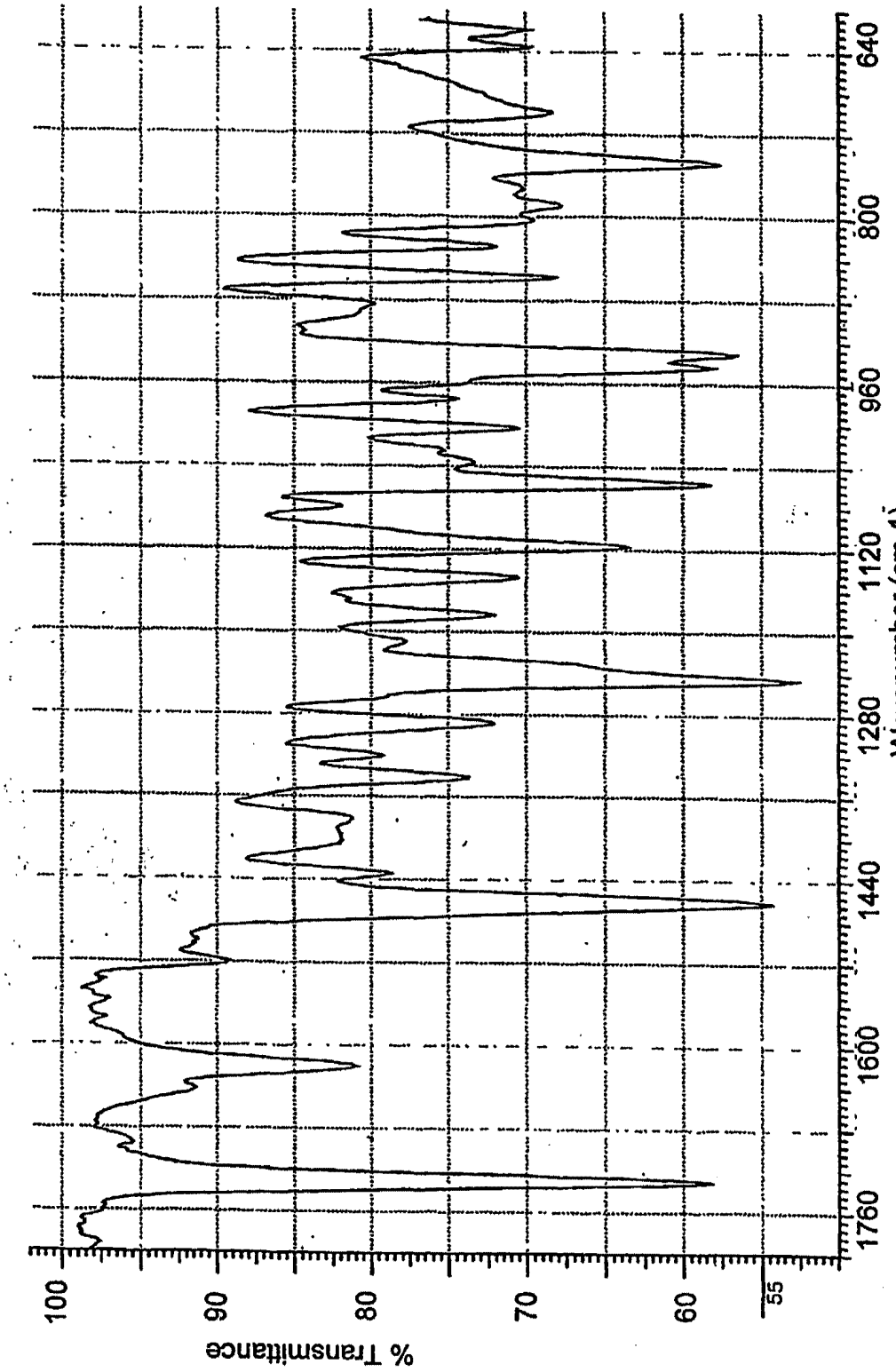

% Transmittance
100
90
80
70
60
55
640
800
960
1120
1280
1440
1600
1760
Wavenumber (cm-1)

FIG. 30

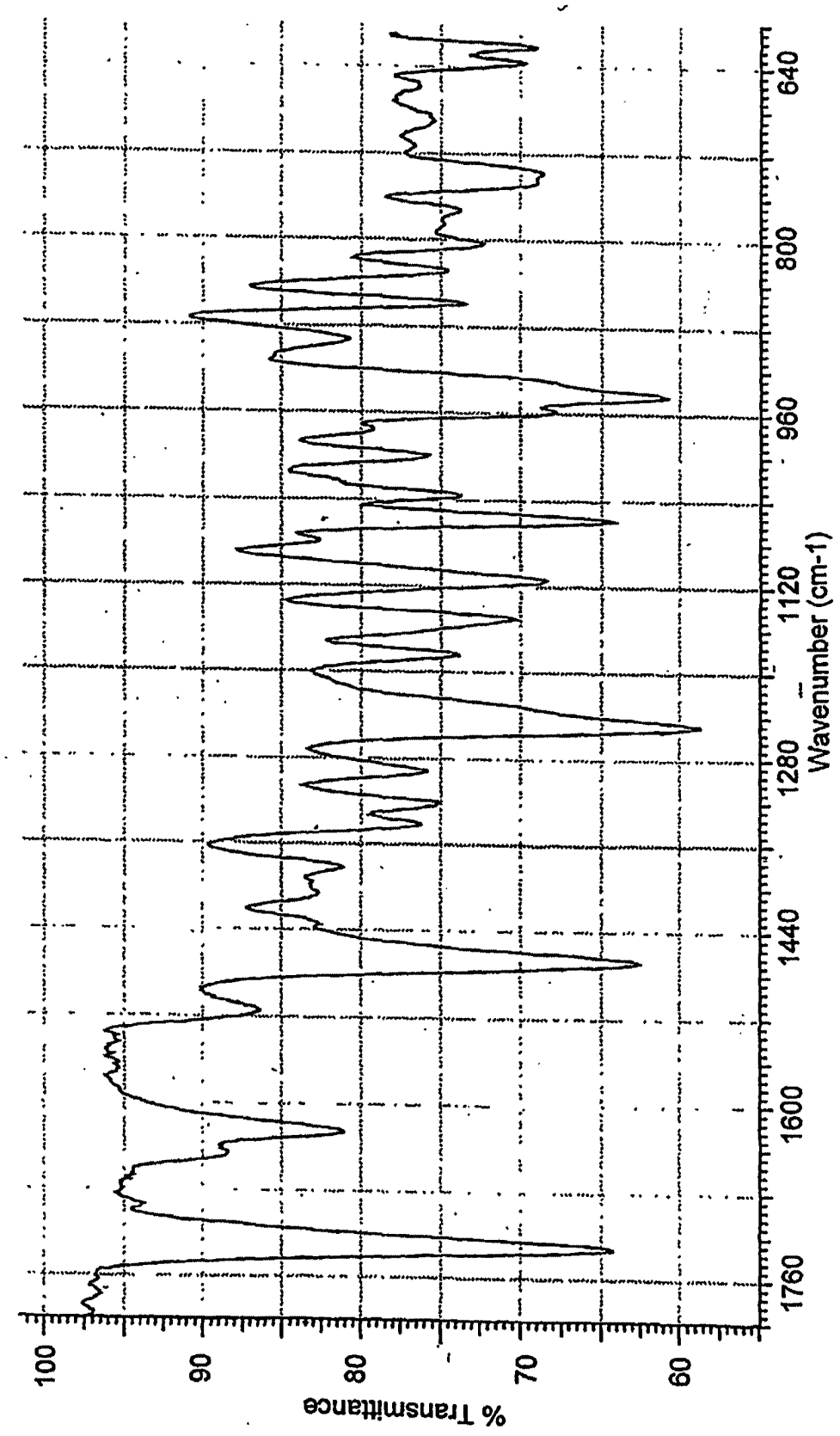

% Transmittance
100
90
80
70
60
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 31A

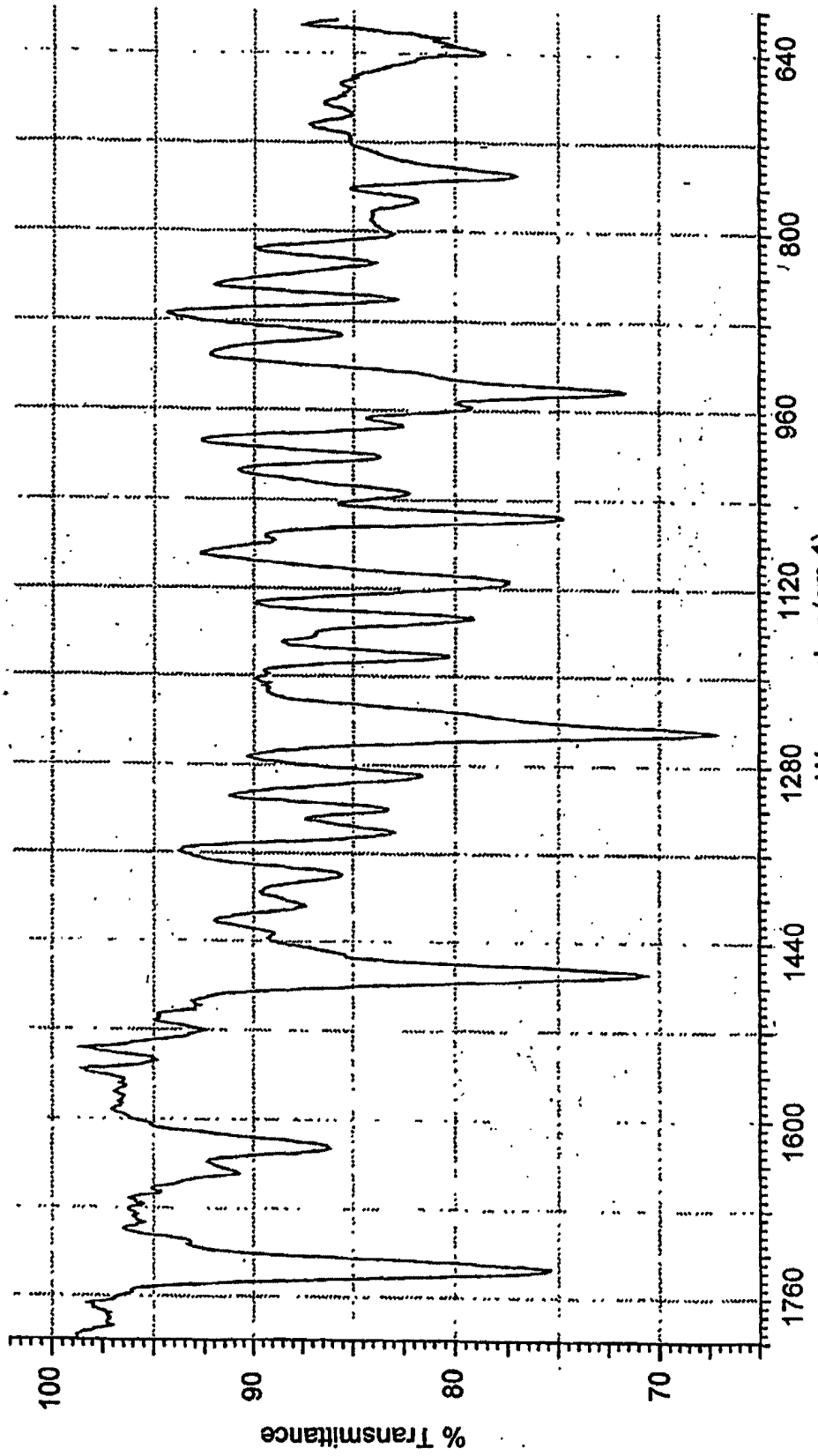

% Transmittance
100
90
80
70
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 31B

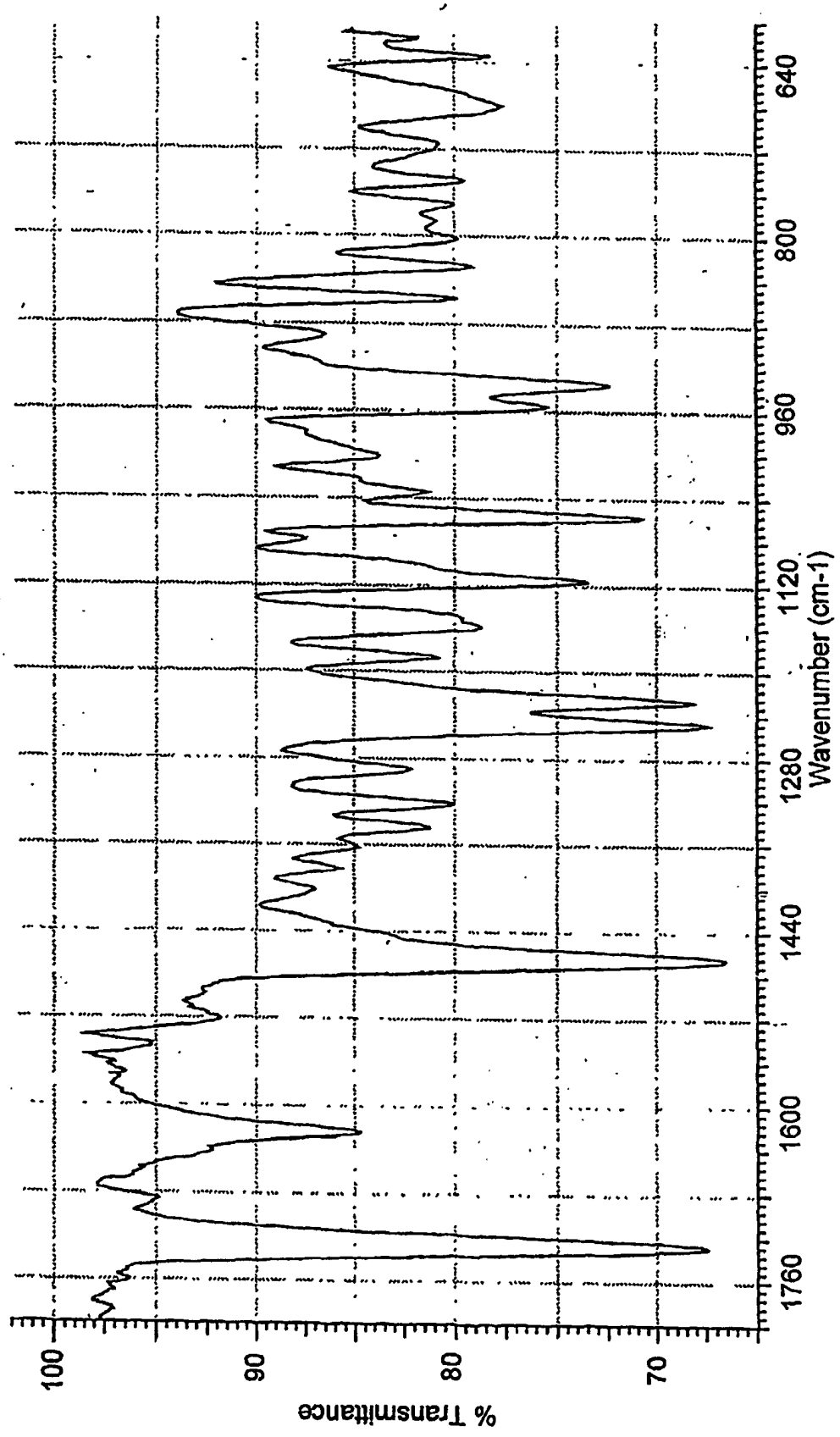

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 32A

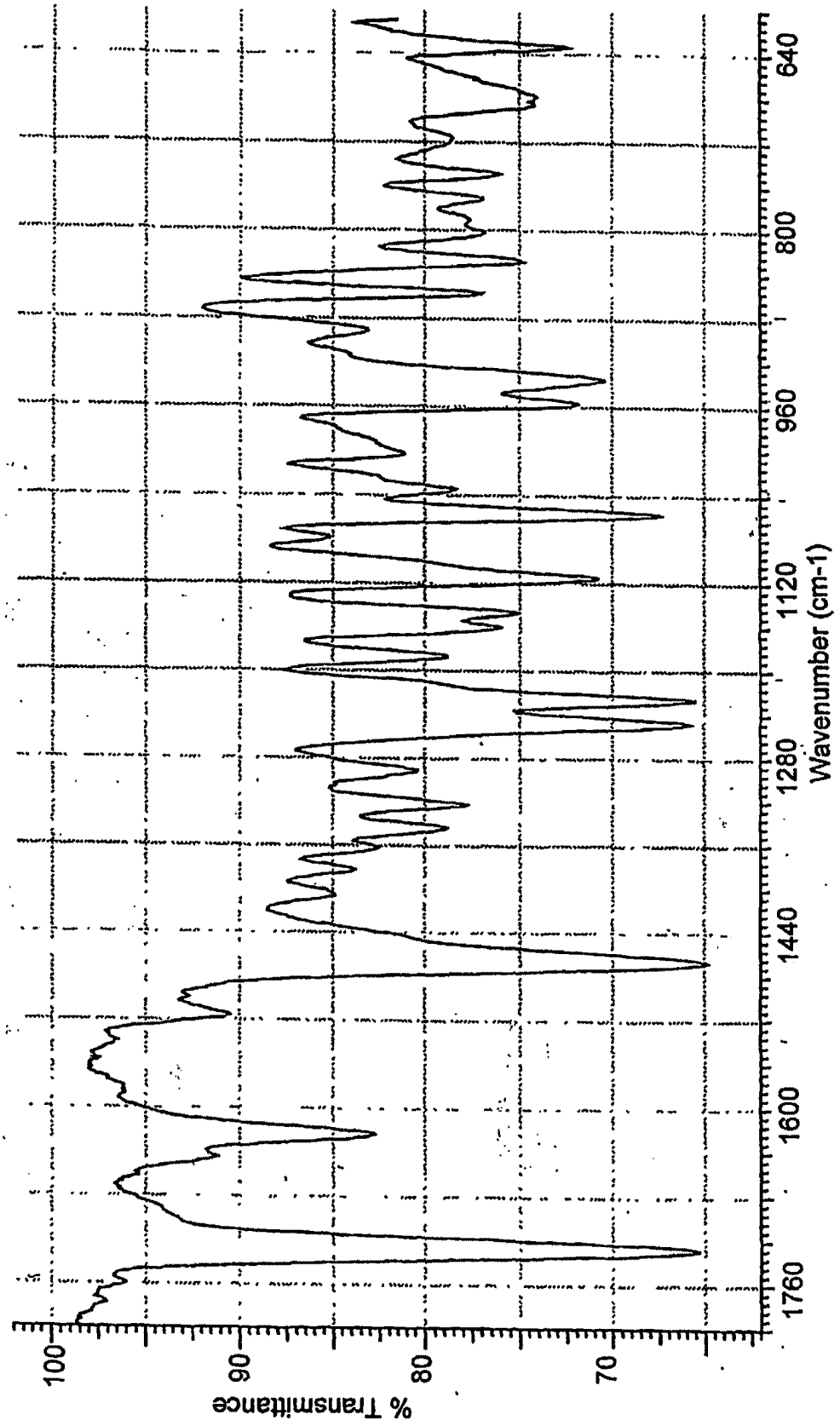

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 32B

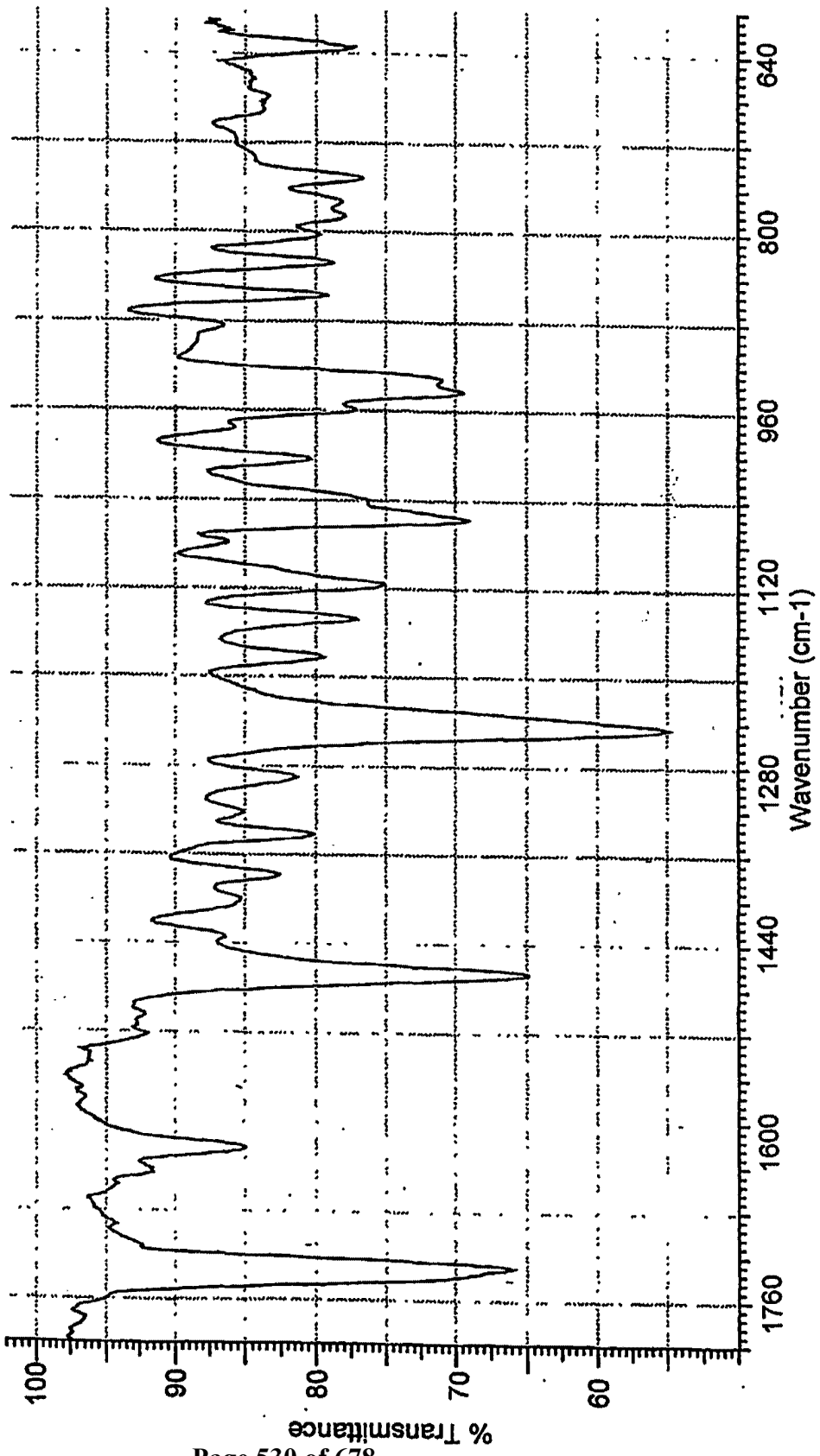

% Transmittance
100
90
80
70
60
640
800
960
1120
1280
1440
1600
1760
Wavenumber (cm-1)

FIG. 33A

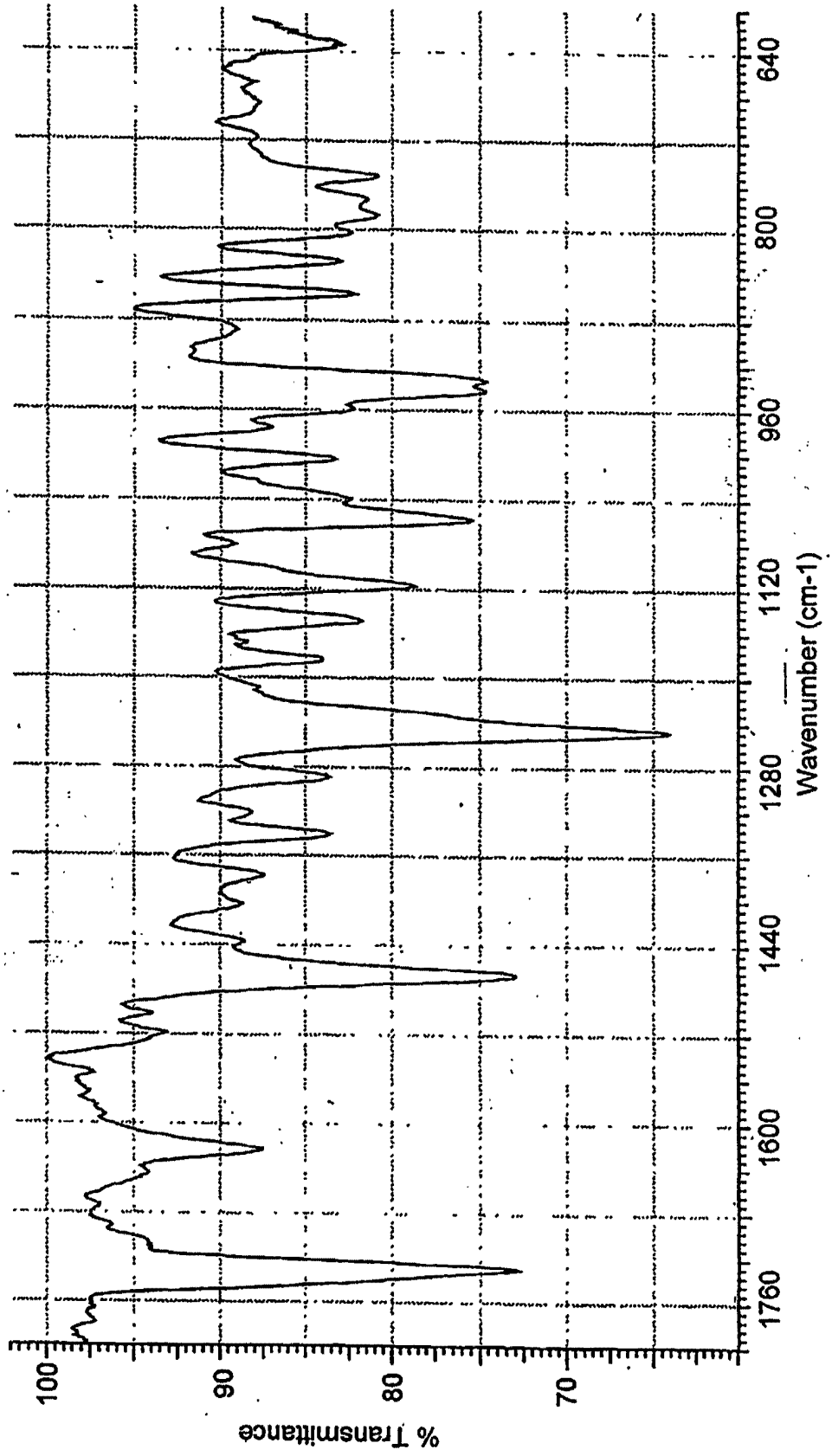

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 33B

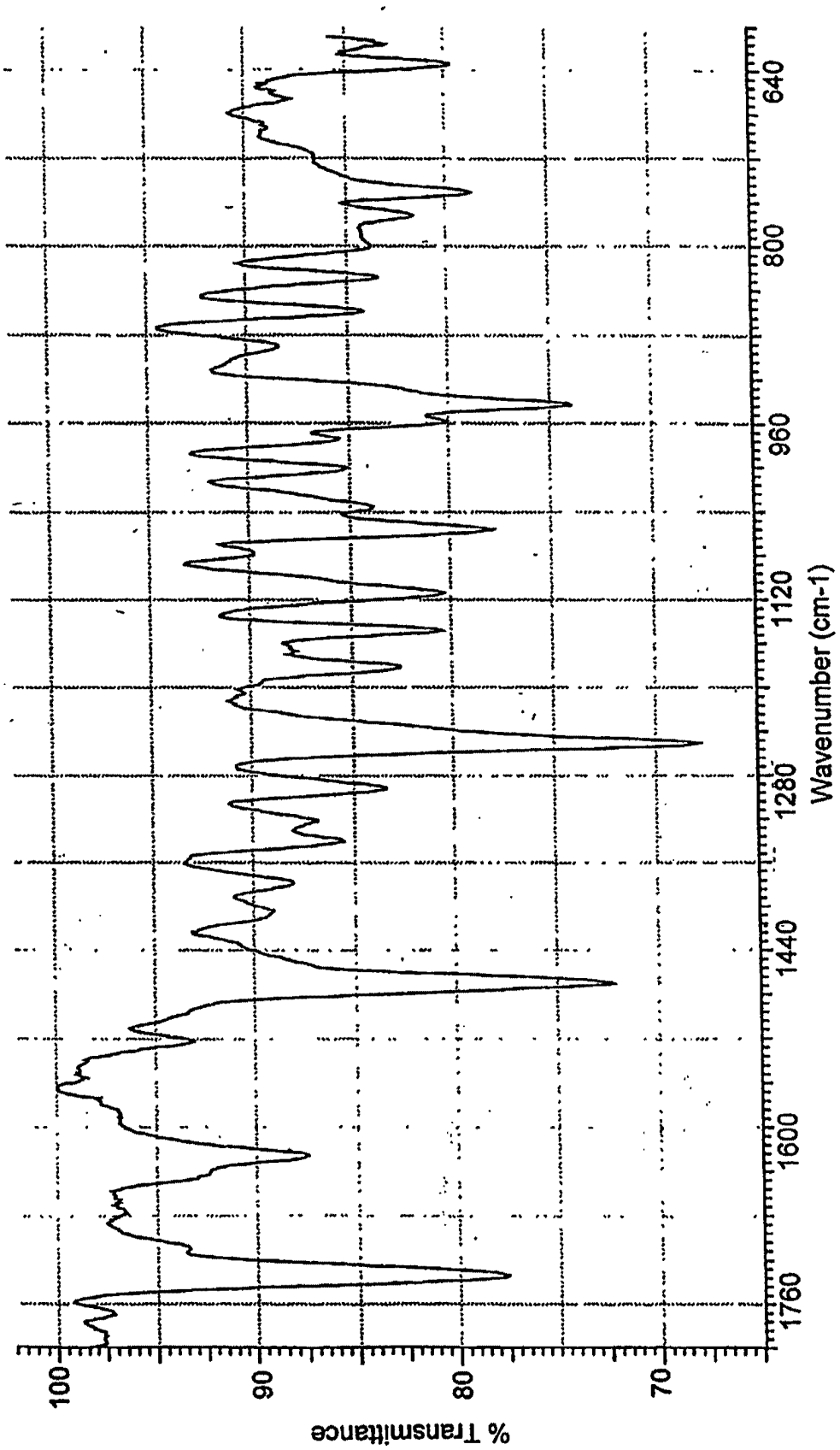

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 34A

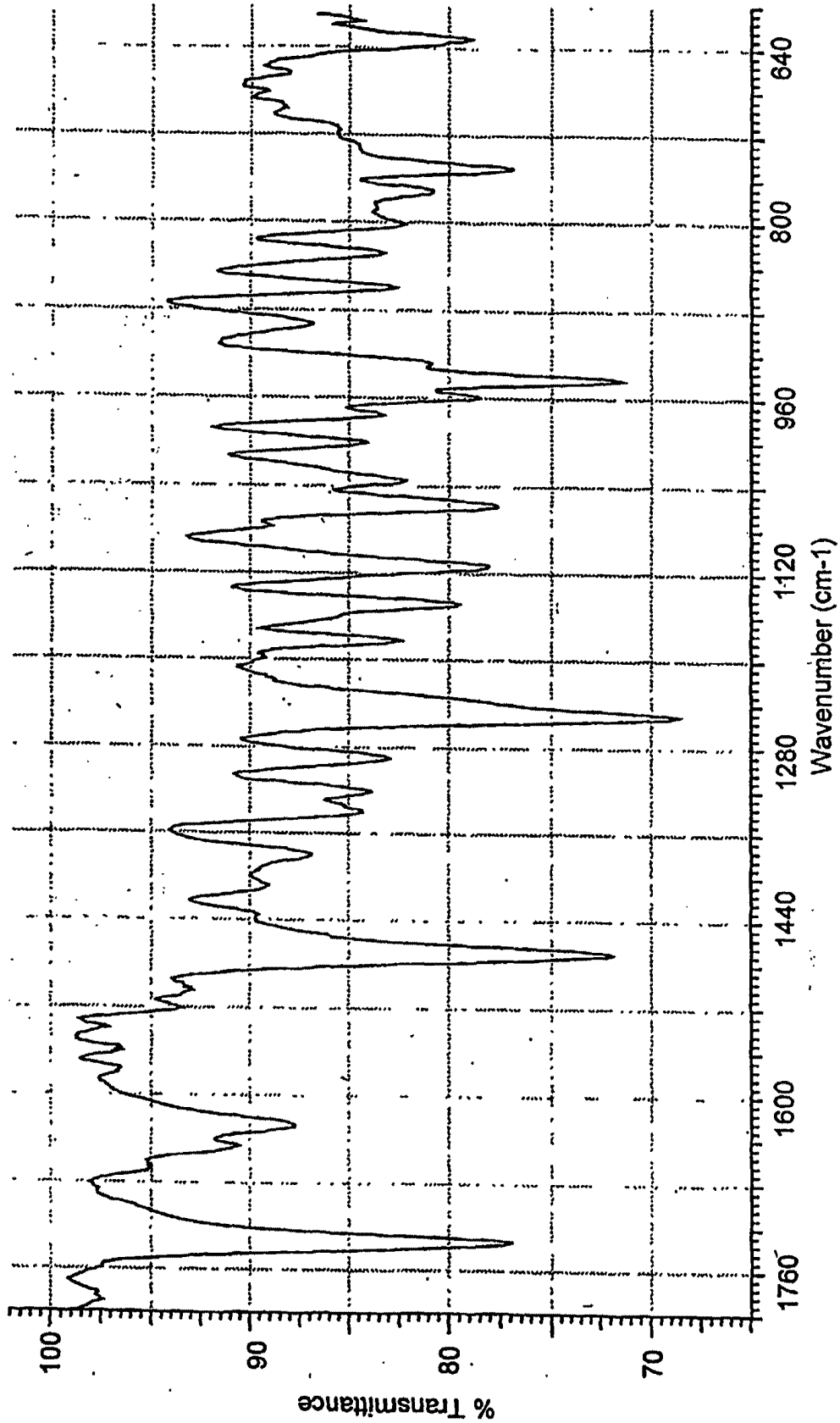

% Transmittance
100
90
80
70
1760
1600
1440
1280
1120
960
800
640
Wavenumber (cm-1)

FIG. 34B

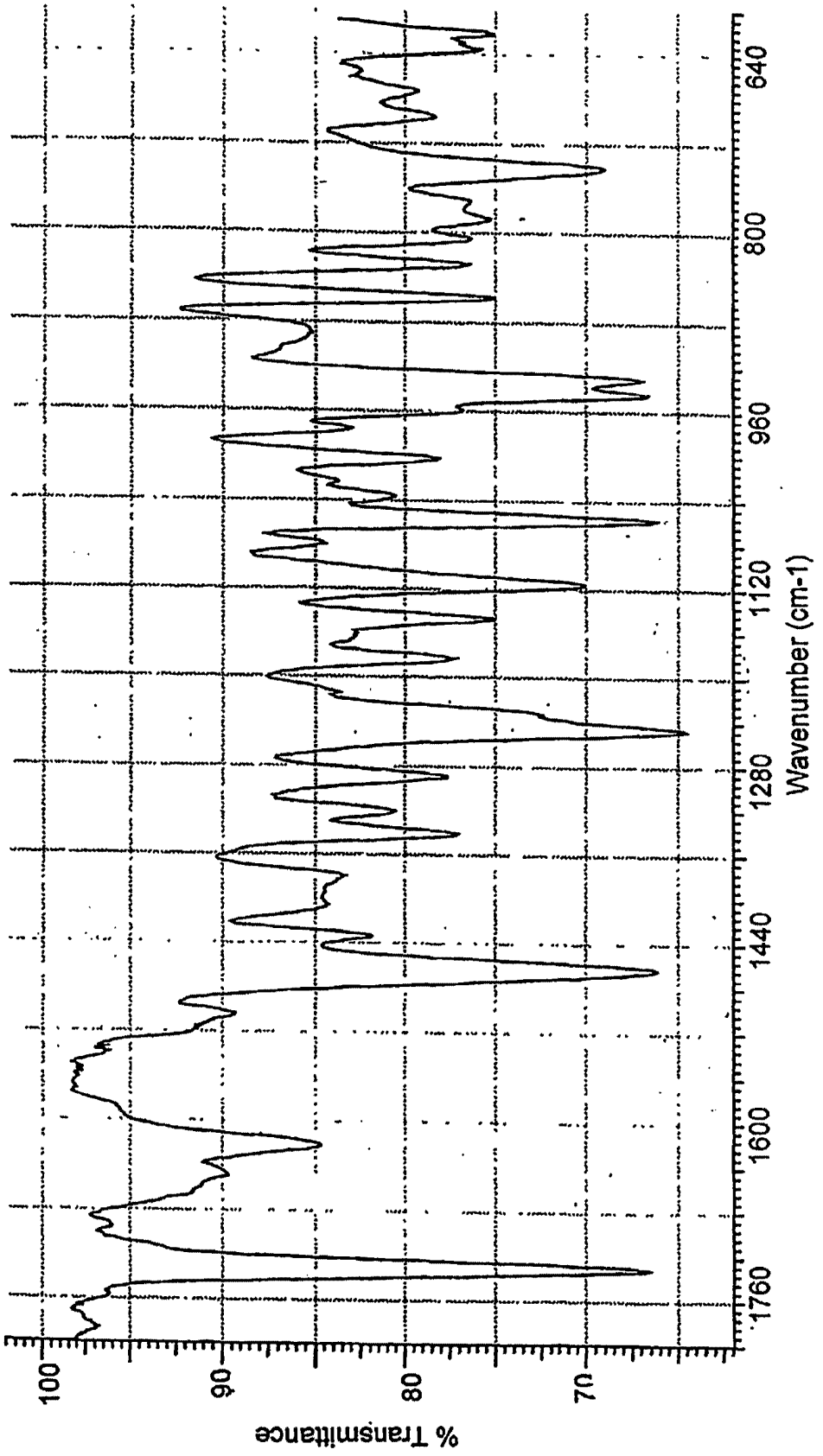

% Transmittance
100
90
80
70
640
800
960
1120
1280
1440
1600
1760
Wavenumber (cm-1)

FIG. 35A

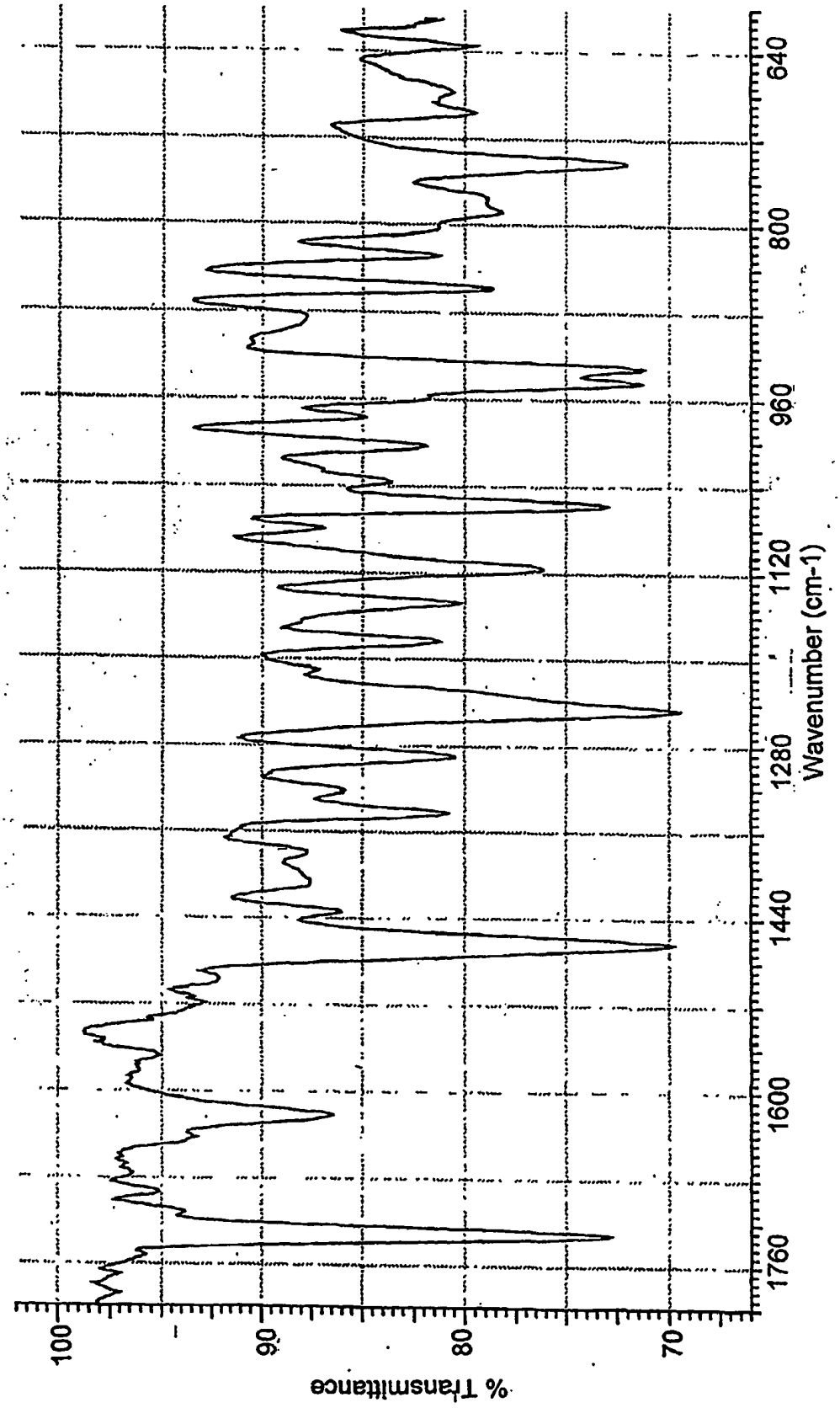

% Transmittance
100
90
80
70
Wavenumber (cm-1)
1760
1600
1440
1280
1120
960
800
640

FIG. 35B

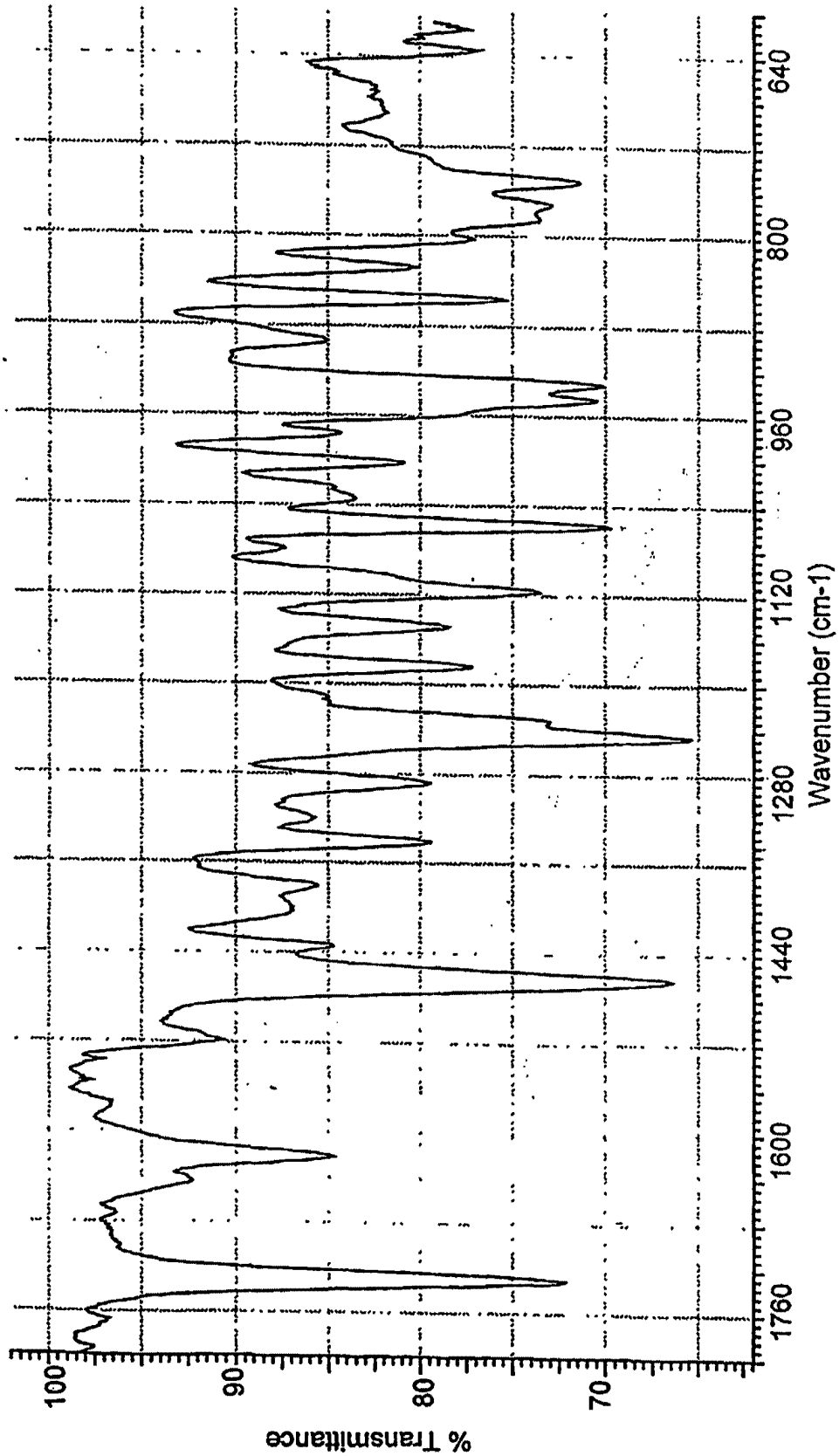

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 36A

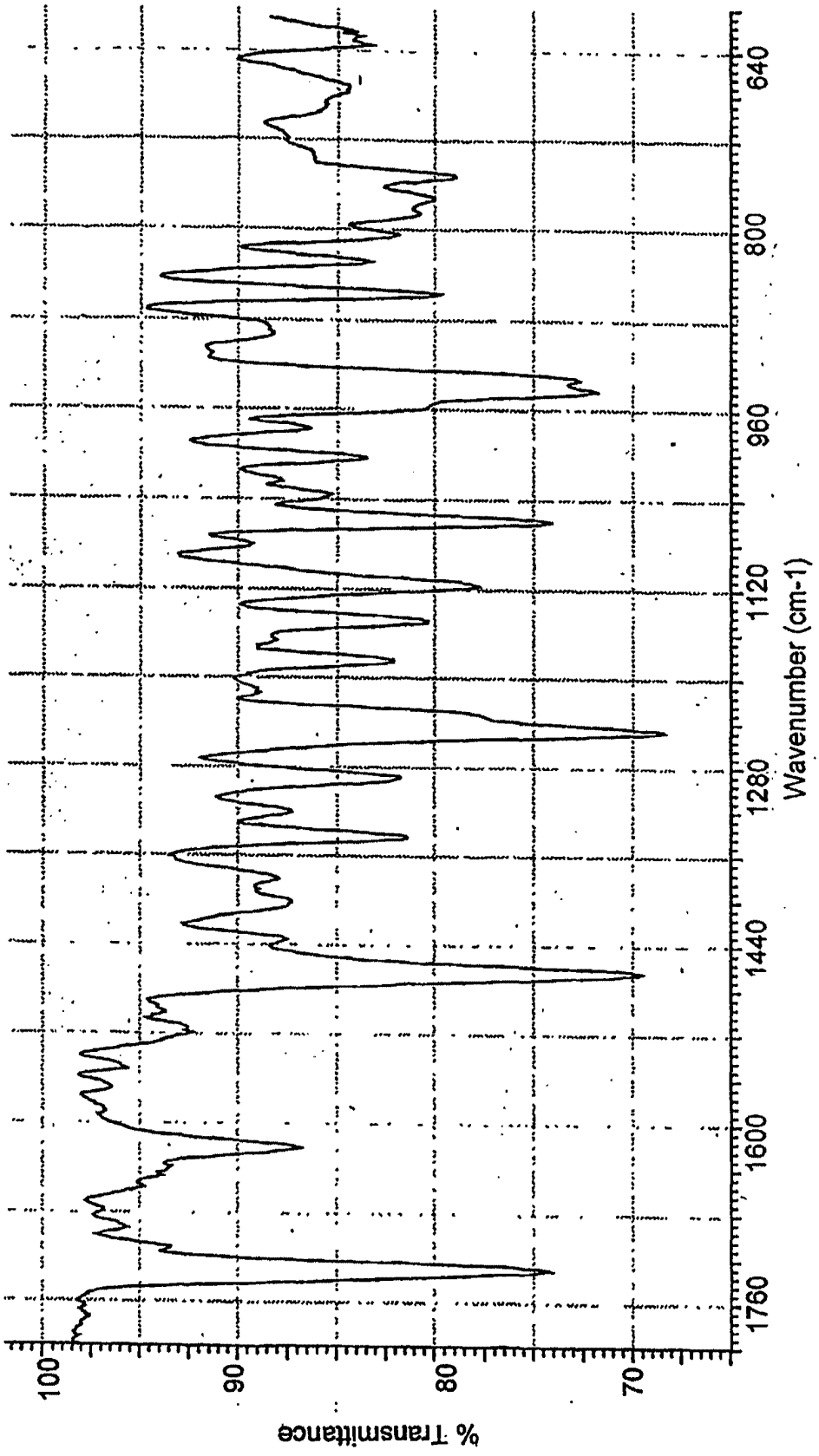

% Transmittance
100
90
80
70
Wavenumber (cm-1)
640
800
960
1120
1280
1440
1600
1760

FIG. 36B

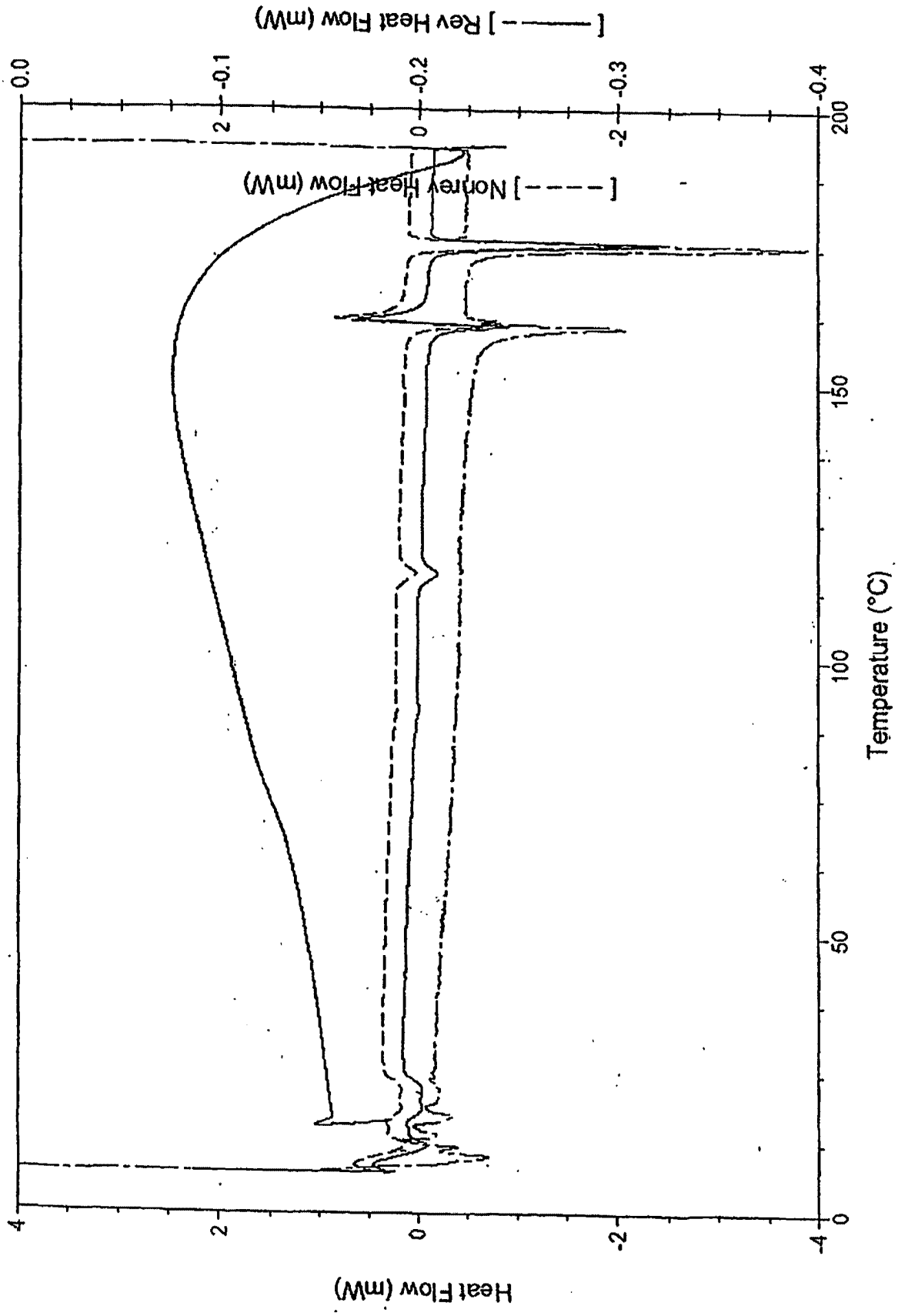

Rev Heat Flow (mW)
Nonrev Heat Flow (mW)
Heat Flow (mW)
Temperature (°C)
0.0
-0.1
-0.2
-0.3
-0.4
2
0
-2
4
2
0
-2
-4
200
150
100
50
0

FIG 37

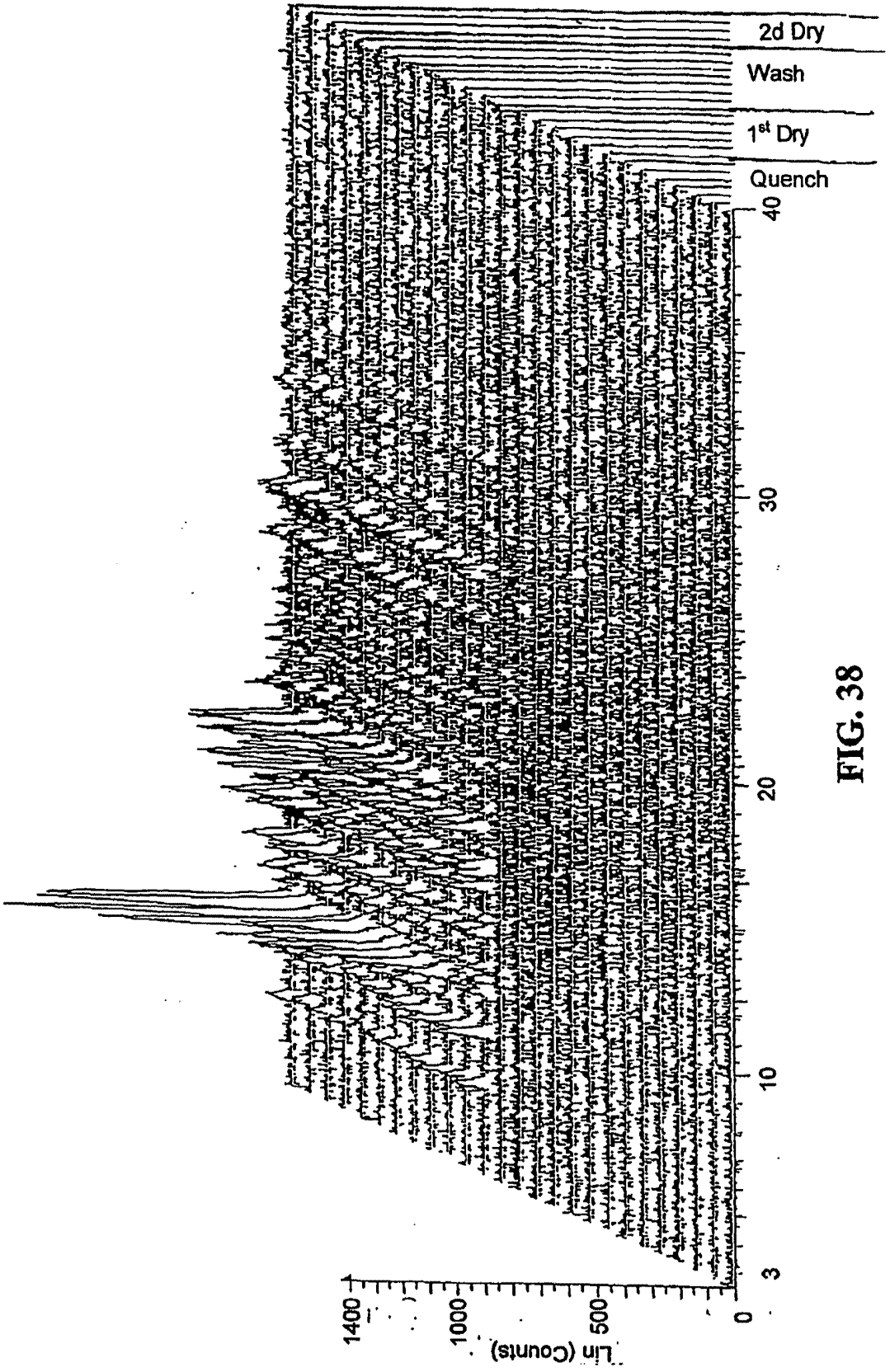

2d Dry
Wash
1st Dry
Quench
40
30
20
10
3
0
500
1000
1400
Lin (Counts)

FIG. 38

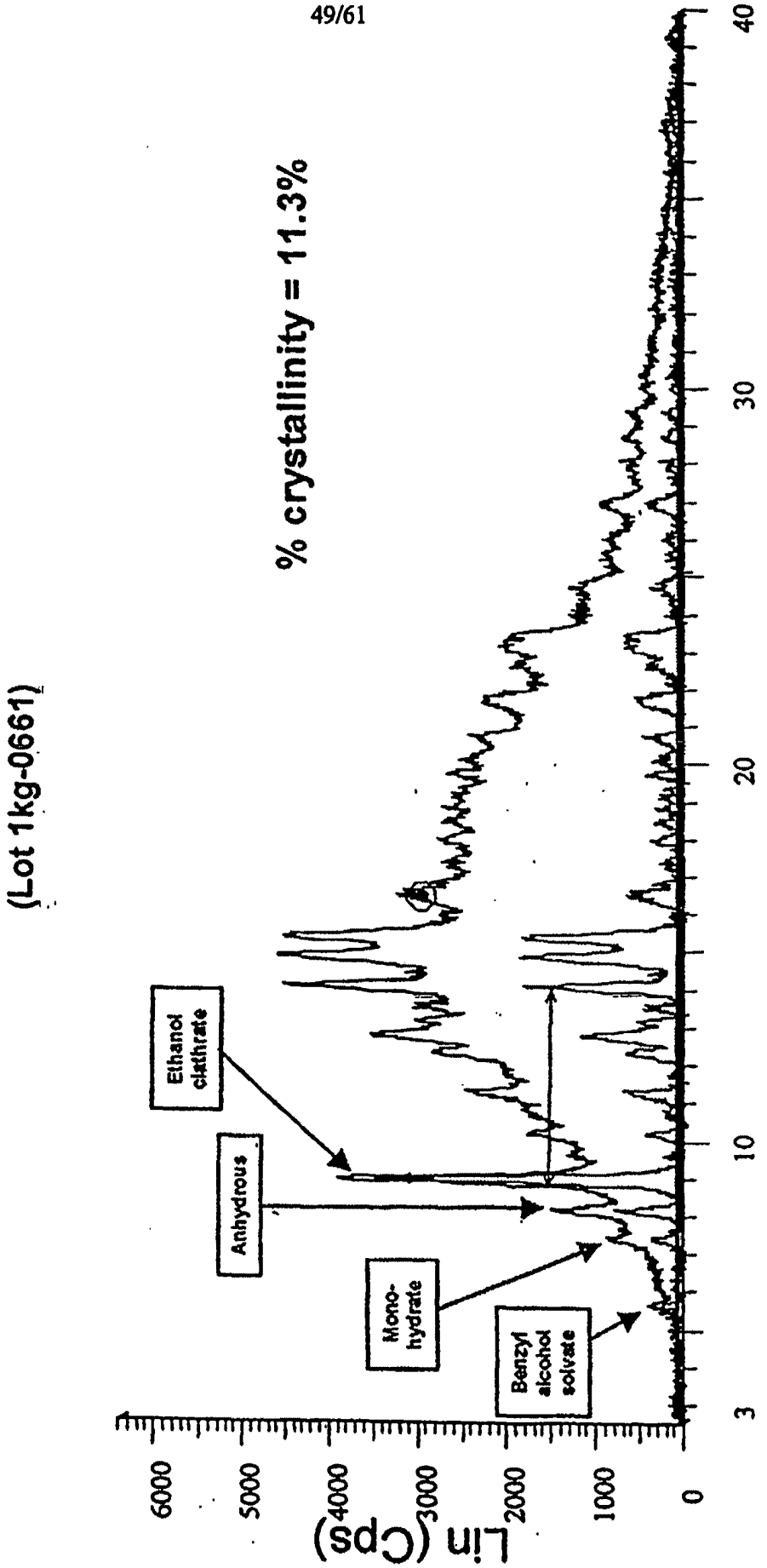

(Lot 1kg-0661)
% crystallinity = 11.3%
Ethanol clathrate
Anhydrous
Mono-hydrate
Benzyl alcohol solvate
Lin (Cps)
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40

FIG. 39

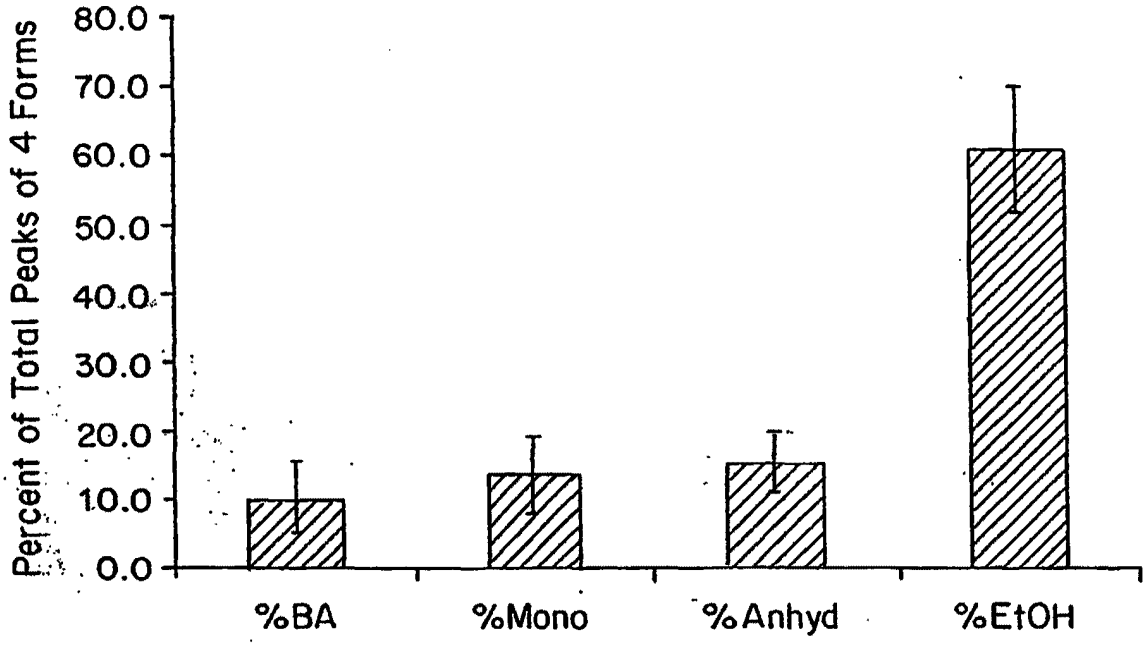

Percent of Total Peaks of 4 Forms
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
%BA
%Mono
%Anhyd
%EtOH

FIG. 40

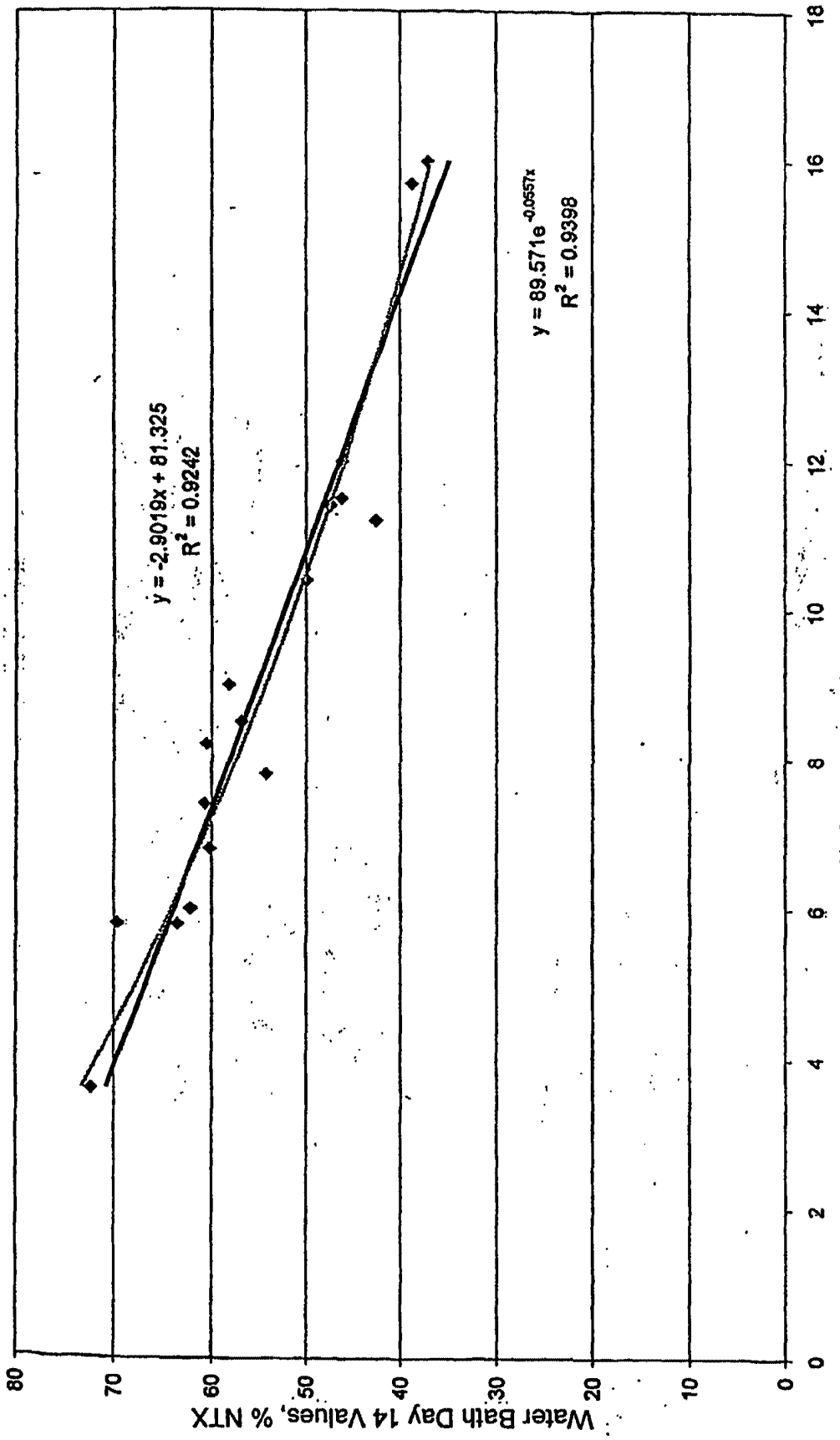

y = -2.9019x + 81.325
R² = 0.9242
y = 89.571e^-0.0557x
R² = 0.9398
Water Bath Day 14 Values, % NTX
% Crystallinity of Microspheres
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18

FIG 41A

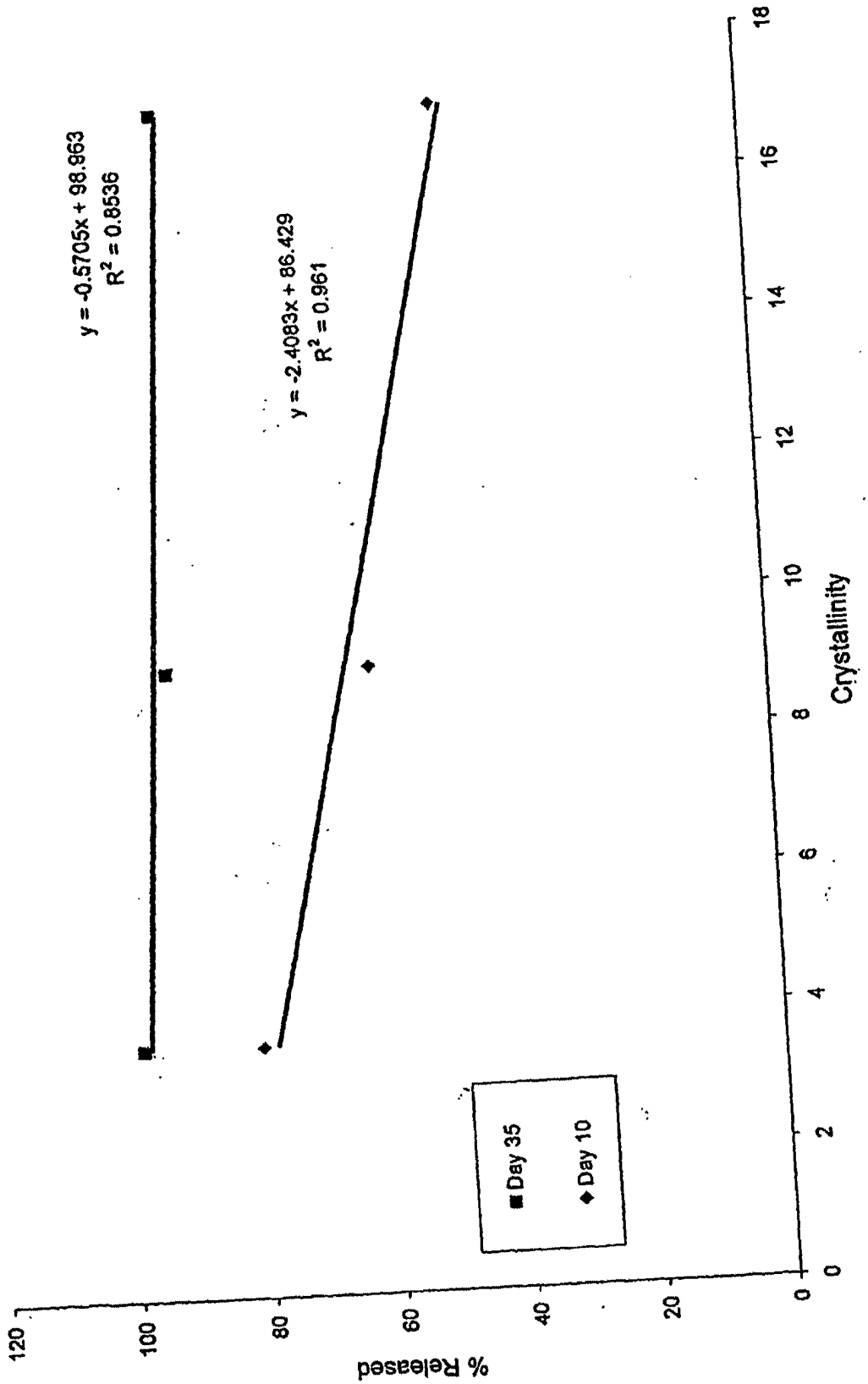

y = -0.5705x + 98.863
R² = 0.8536
y = -2.4083x + 86.429
R² = 0.961
Day 35
Day 10
% Released
Crystallinity
0
20
40
60
80
100
120
0
2
4
6
8
10
12
14
16
18

FIG 41B

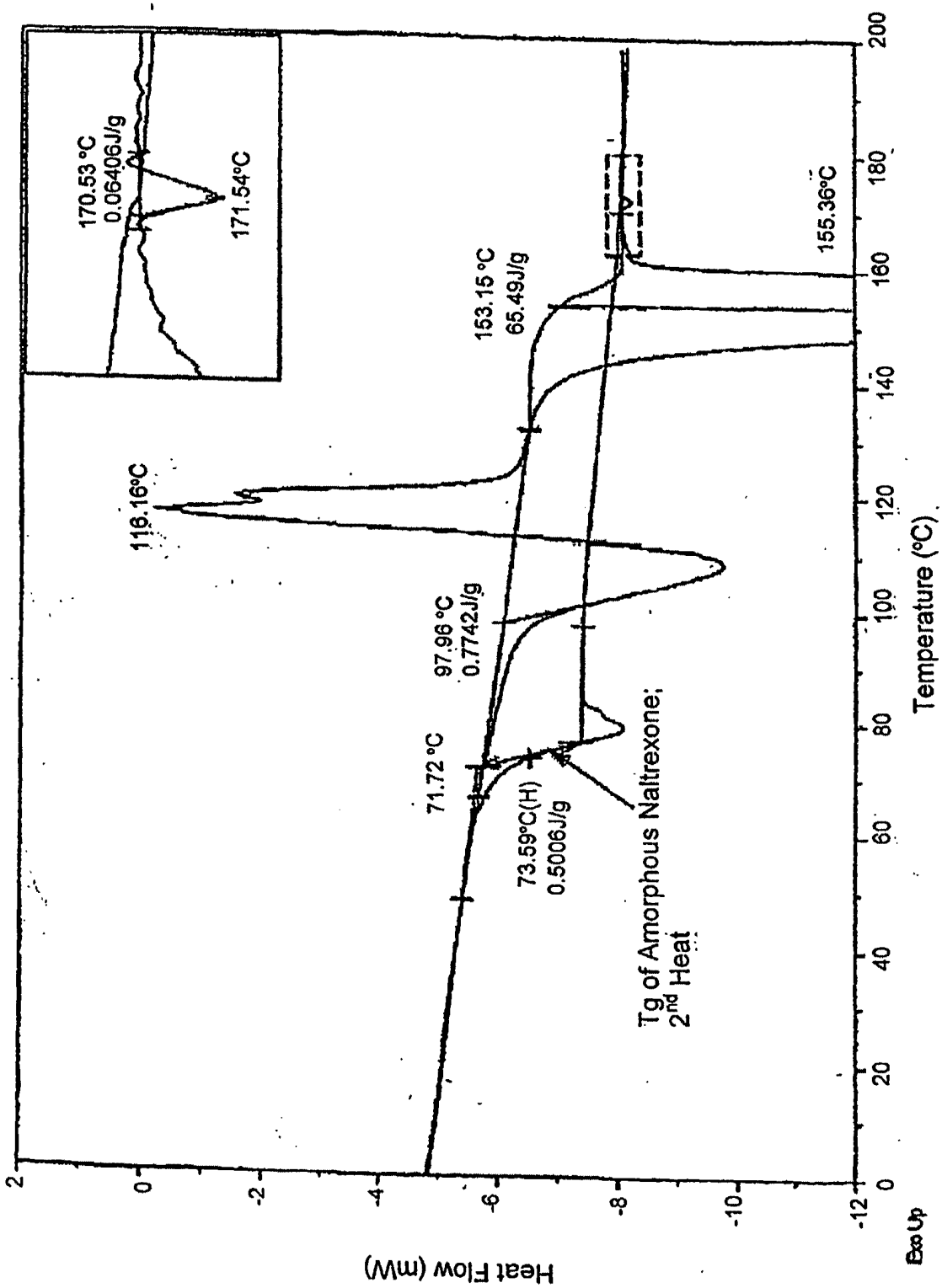

170.53 °C
0.0640GJ/g
171.54°C
153.15 °C
65.49J/g
155.36°C
116.16°C
97.96 °C
0.7742J/g
71.72 °C
73.59°C(H)
0.5006J/g
Tg of Amorphous Naltrexone;
2nd Heat
Heat Flow (mW)
Temperature (°C)
Exo Up

FIG 42

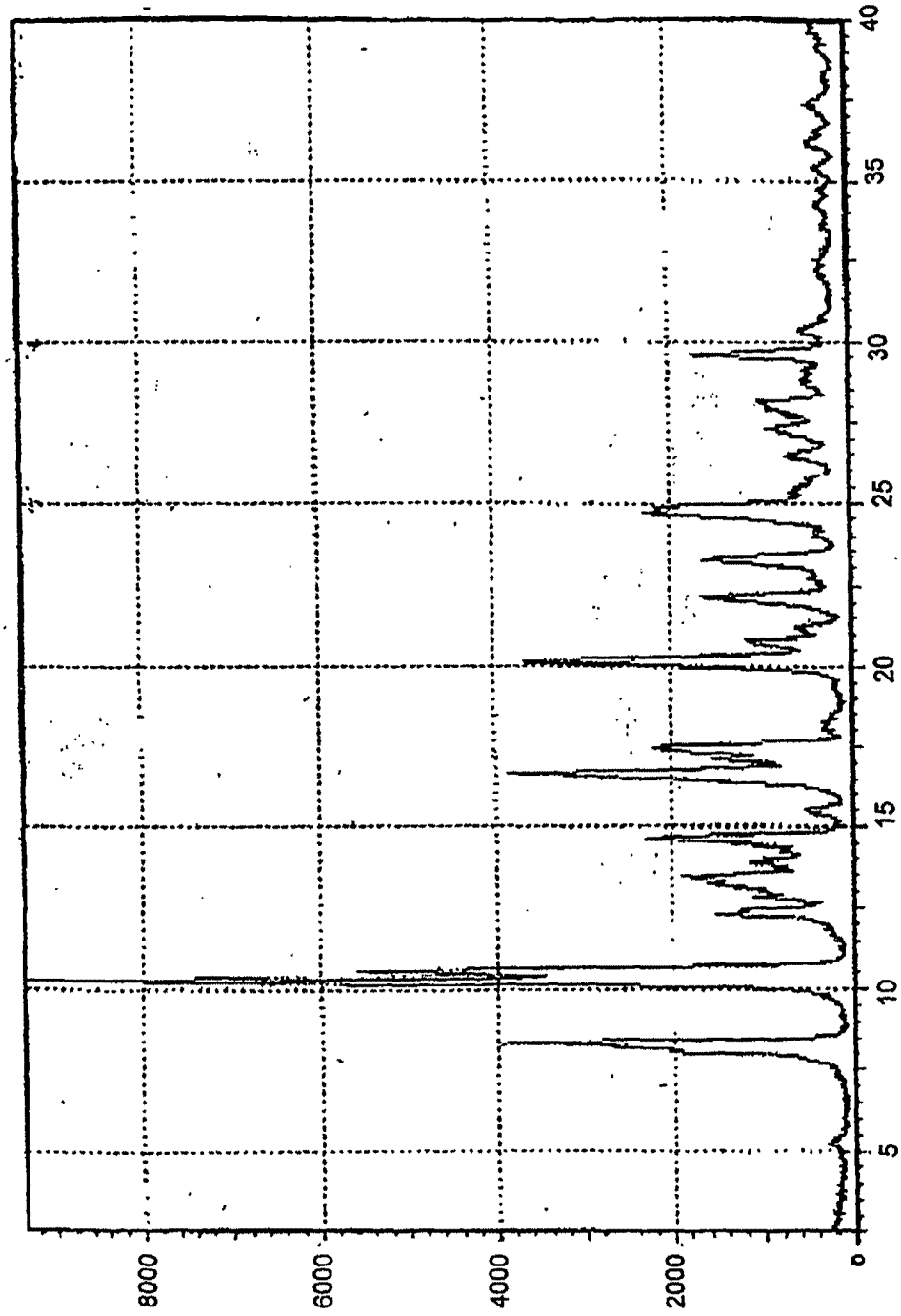


FIG. 43

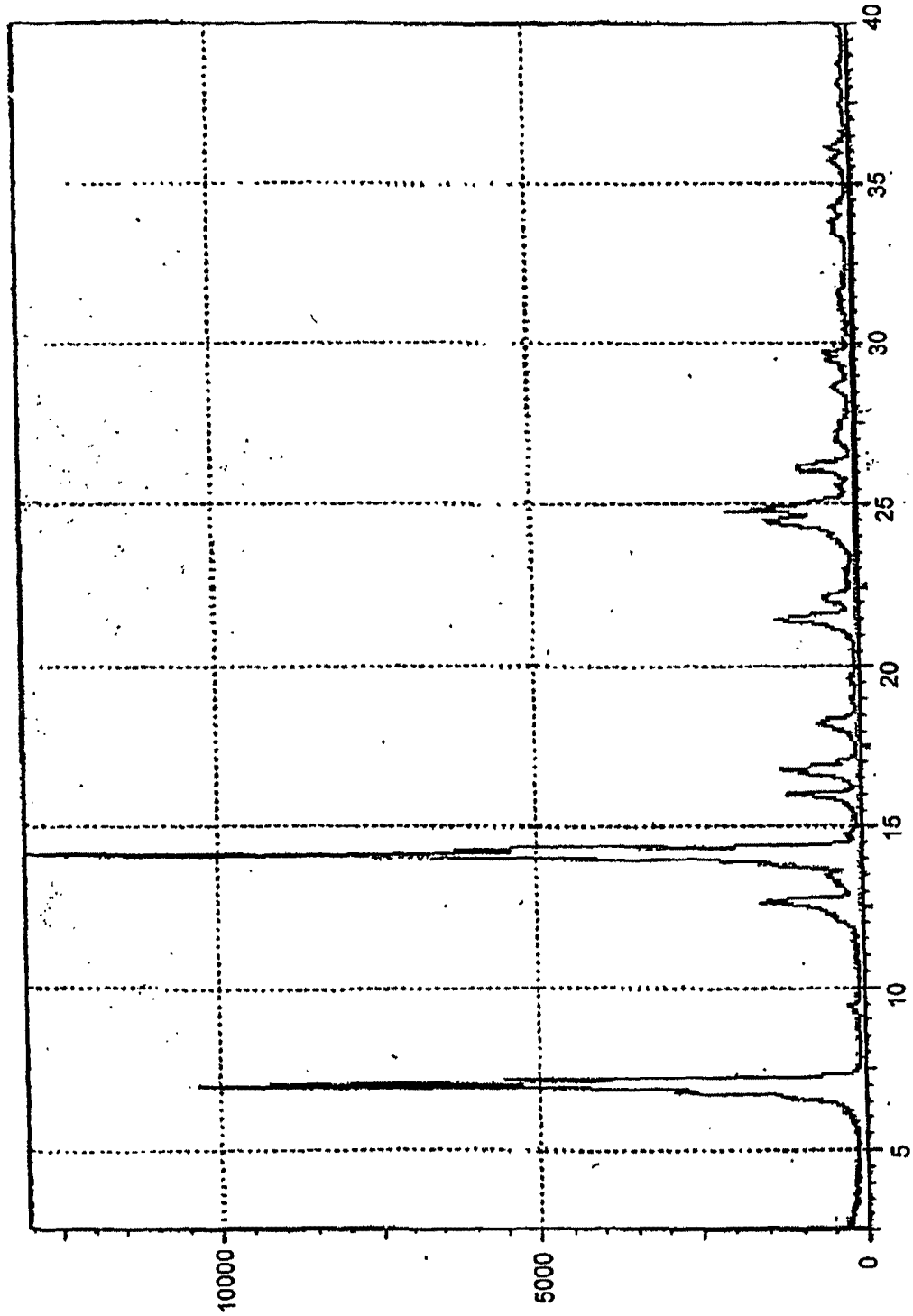


FIG. 44

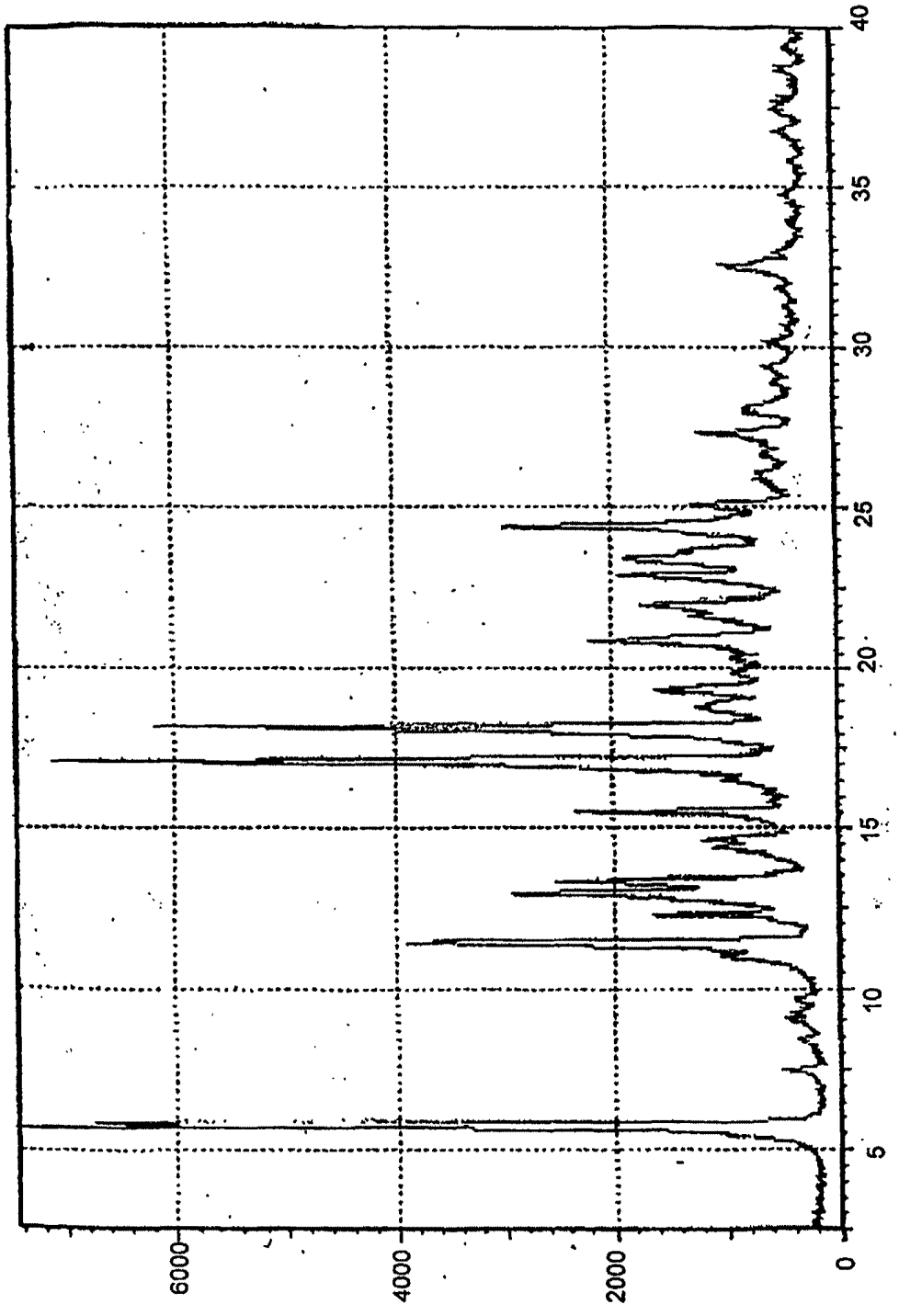


FIG. 45

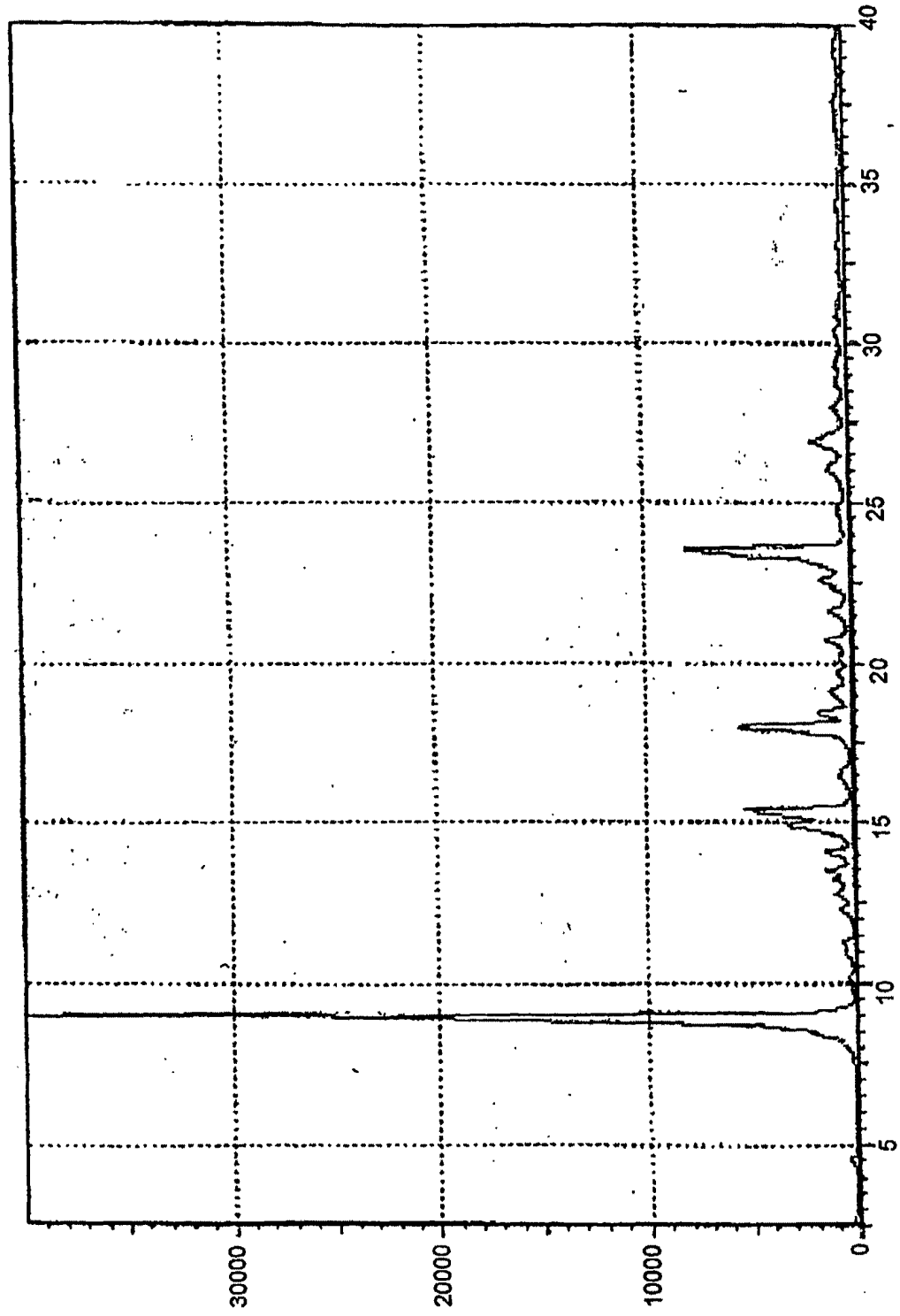


FIG. 46

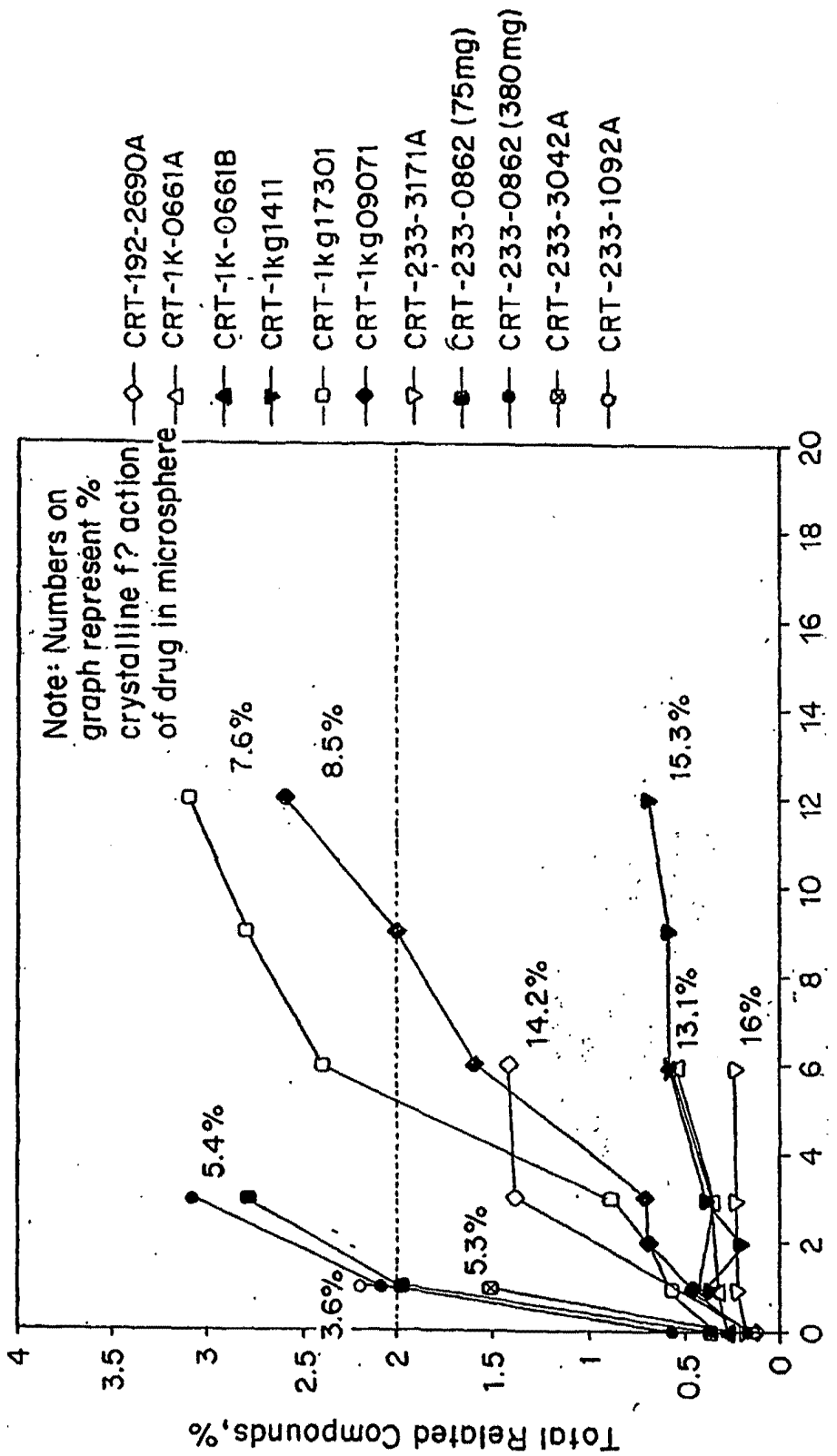

Note: Numbers on graph represent % crystalline f? action of drug in microsphere
CRT-192-2690A
CRT-1K-0661A
CRT-1K-0661B
CRT-1kg1411
CRT-1kg17301
CRT-1kg09071
CRT-233-3171A
CRT-233-0862 (75mg)
CRT-233-0862 (380mg)
CRT-233-3042A
CRT-233-1092A
5.4%
7.6%
8.5%
3.6%
5.3%
14.2%
15.3%
13.1%
16%
Total Related Compounds,%
time,months
0
0.5
1
1.5
2
2.5
3
3.5
4
0
2
4
6
8
10
12
14
16
18
20

FIG. 47

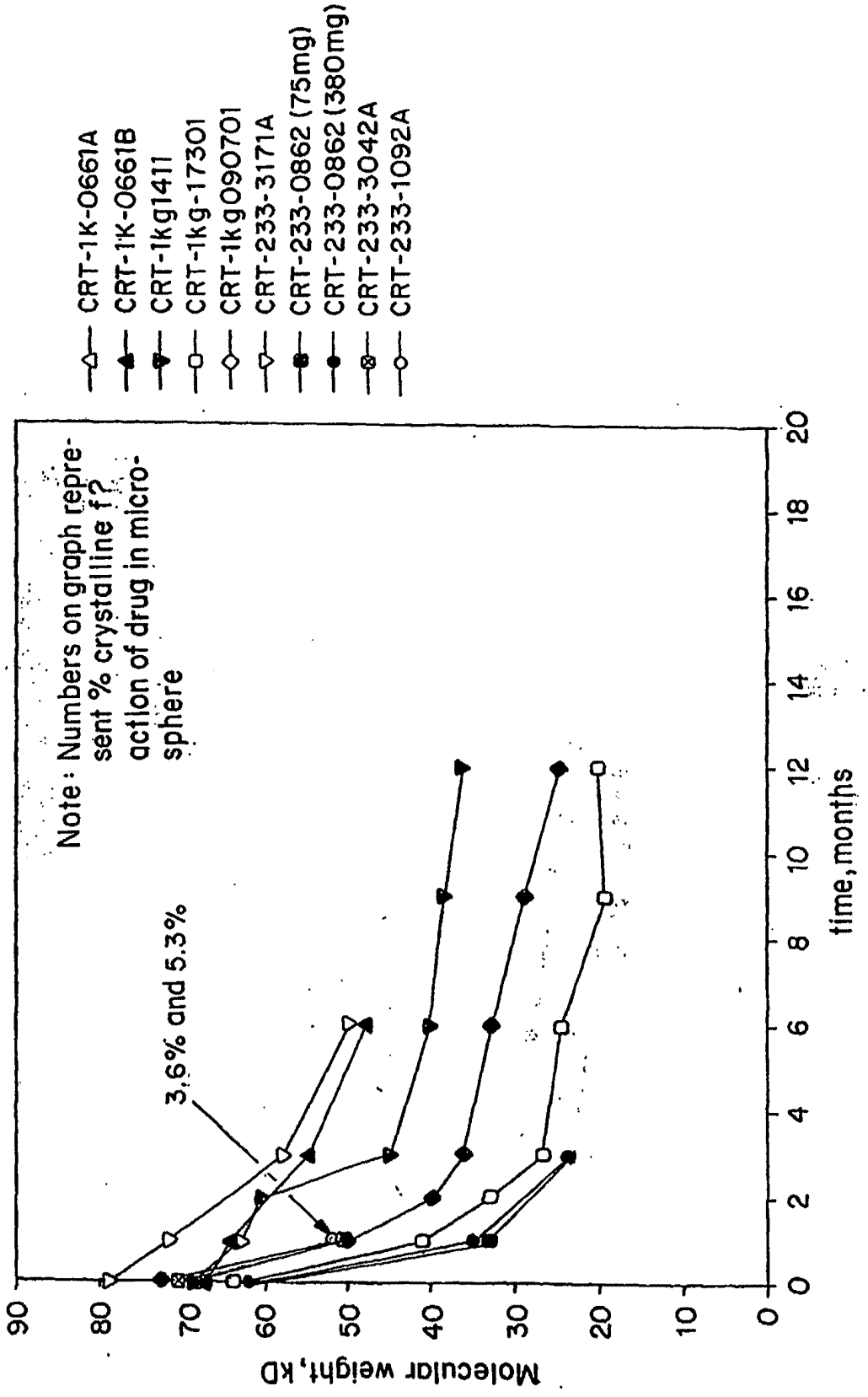

CRT-1K-0661A
CRT-1K-0661B
CRT-1kg1411
CRT-1kg-17301
CRT-1kg090701
CRT-233-3171A
CRT-233-0862 (75mg)
CRT-233-0862 (380mg)
CRT-233-3042A
CRT-233-1092A
Note: Numbers on graph represent % crystalline fraction of drug in microsphere
3,6% and 5.3%
Molecular weight, kD
time, months
0
10
20
30
40
50
60
70
80
90
0
2
4
6
8
10
12
14
16
18
20

FIG. 48

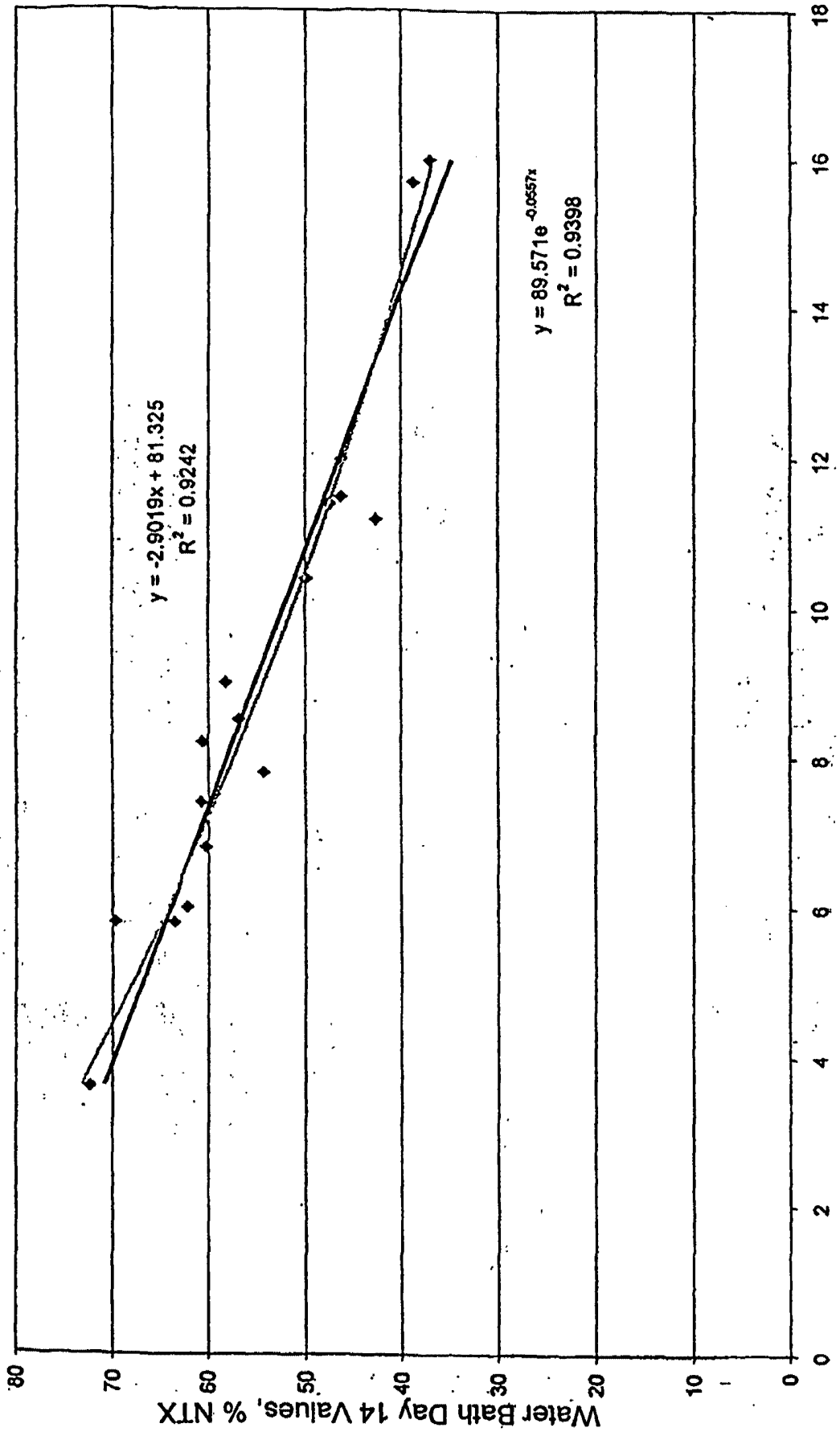

y = -2.9019x + 81.325
R² = 0.9242
y = 89.571e^-0.0557x
R² = 0.9398
Water Bath Day 14 Values, % NTX
% Crystallinity of Microspheres
0
10
20
30
40
50
60
70
80
0
2
4
6
8
10
12
14
16
18

FIG. 49A

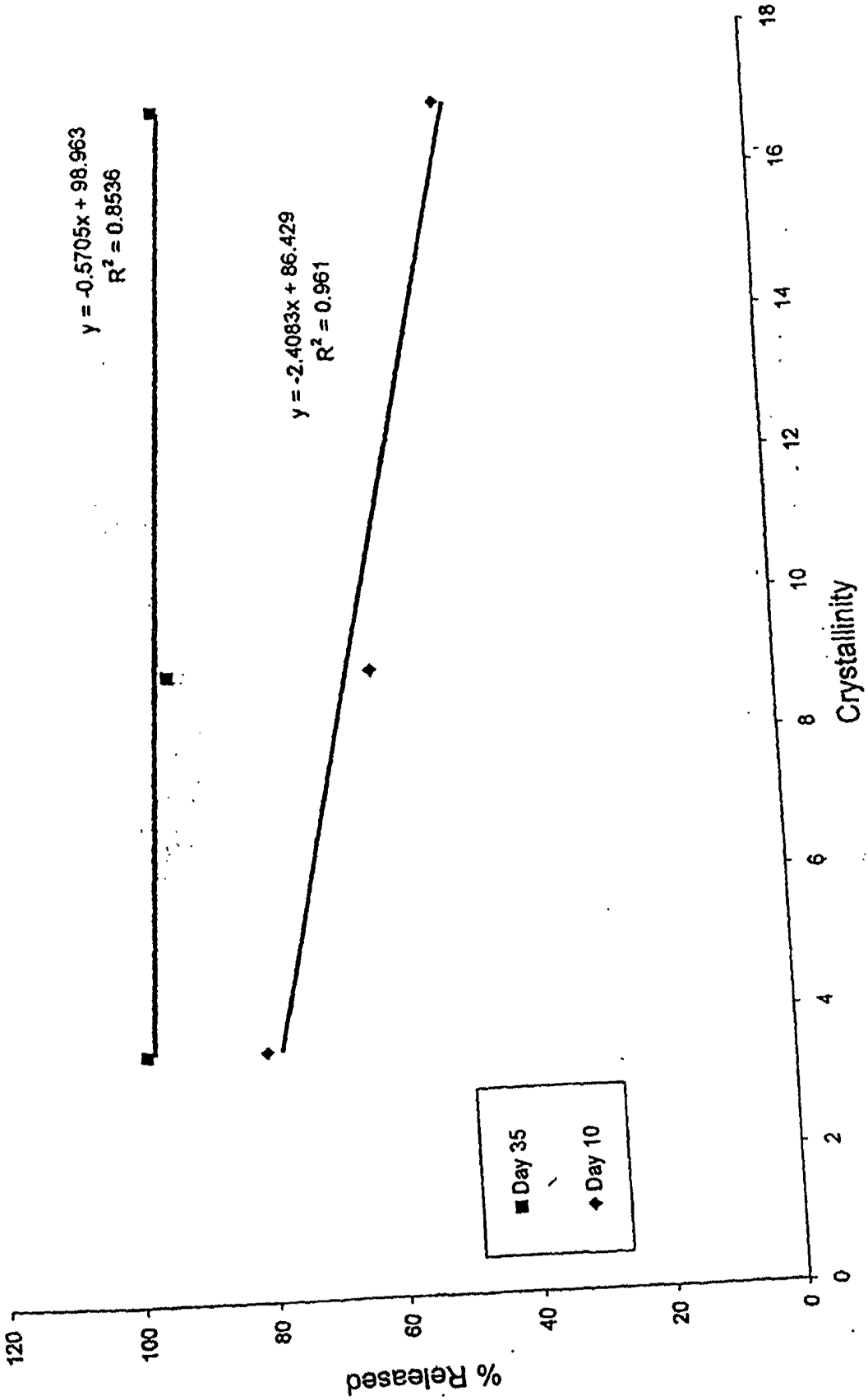

y = -0.5705x + 98.963
R² = 0.8536
y = -2.4083x + 86.429
R² = 0.961
Day 35
Day 10
% Released
Crystallinity
0
20
40
60
80
100
120
0
2
4
6
8
10
12
14
16
18

FIG. 49B

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108084 A3

(51) International Patent Classification[7]: A61K 31/485

(21) International Application Number: PCT/US2004/017496

(22) International Filing Date: 3 June 2004 (03.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/475,863 4 June 2003 (04.06.2003) US

(71) Applicant *(for all designated States except US)*: **ALKERMES CONTROLLED THERAPEUTICS, II** [US/US]; 88 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRITTAIN, Harry, A.** [US/US]; 10 Charles Road, Milford, NJ 08858 (US). **DICKASON, David, A.** [US/US]; 4739 Vicbarb Lane, Cincinnati, OH 45244 (US). **HOTZ, Joyce** [US/US]; 8219 Pinecone Court, Cincinnati, OH 45249 (US). **LYONS, Shawn, L.** [US/US]; 1113 Alcliff Lane, Cincinnati, OH 45238 (US). **RAMSTACK, Michael, J.** [US/US]; 44 Cortland Circle, Lunenburg, MA 01462 (US). **WRIGHT, Steven, G.** [US/US]; 7012 Juniperview Lane, Madeira, OH 45243 (US).

(74) Agents: **ELMORE, Carolyn, S.** et al.; Elmore Craig, P.C., 209 Main Street, Chelmsford, MA 01863 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 17 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/108084 A3

(54) Title: POLYMORPHIC FORMS OF NALTREXONE

(57) Abstract: This invention relates to the discovery of novel polymorphic forms of naltrexone, including solvates, hydrates, anhydrous and other crystalline forms and combinations thereof. These novel forms of naltrexone impart advantages in pharmaceutical formulations incorporating them, including sustained release, or long acting, formulations.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/17496

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/485
US CL : 514/282, 326
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/282, 326

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- X	US 6,264,987 B1 (WRIGHT et al .) 24 July 2001 (24.07.2001), col. 8 ,lines 45-47, col. 7, lines 63-65.	47-60 --- 13-16
X	US 6,277,859 B1 (NAGASE et al) 21 August 2001 (21.08.2001), col. 81, lines 18-20).	17-19
X	US 4,141,897 A (OLOFSON et al.) 27 February 1979 (27.02.1979), col. 20 ,lines 55-57.	26-28
X --- Y	US 6,228,863 B1 (PALERMO et al.) 08 May 2001 (08.05.2001), col. 26, lines 50-55.	1-12, 20-22, and 26-28 --- 47-60

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search
30 October 2004 (30.10.2004)

Date of mailing of the international search report
14 DEC 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Taylor V. Oh
Telephone No. 571-272-2717

Form PCT/ISA/210 (second sheet) (January 2004)

Continuation of B. FIELDS SEARCHED Item 3:
West search done :polymorph, naltrexone, toluene, hexane, acetone, ethylacetate, methanol, dichloromethane, ethanol, acetone, dimethylformamide, benzyl acohol, ethanolate.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
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(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/001501

(22) International Filing Date: 21 January 2004 (21.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/441,946 22 January 2003 (22.01.2003) US

(71) Applicant *(for all designated States except US)*: **ALKERMES CONTROLLED THERAPEUTICS, INC.** [US/US]; 88 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROWN, Josiah** [US/US]; 60 Elm Street #2, Somerville, MA 02144 (US). **JAWOROWICZ, Warren, E.** [US/US]; 383 South Bolton Road, Bolton, MA 01740 (US). **TROIANO, Gregory, C.** [US/US]; 17 Elinor Road, Weymouth, MA 02190 (US).

(74) Agents: **BROOK, David, E.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/064752 A2

(54) Title: METHOD OF PREPARING SUSTAINED RELEASE MICROPARTICLES

(57) Abstract: The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent. The invention provides an improved process for the preparation of microparticles, wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/drug matrix. The method includes the steps of (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/drug matrix can be provided by any suitable method.

METHOD OF PREPARING SUSTAINED RELEASE MICROPARTICLES

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/441,946, filed January 22, 2003, the entire contents of which are incorporated herein by reference.

GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by a grant (Grant No. 1 R43 DA13531-01A1) from the National Institute on Drug Abuse (NIDA) at the National Institutes of Health (NIH). The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Many illnesses or conditions require administration of a constant or sustained level of a medicament or biologically active agent to provide the desired prophylactic or therapeutic effect. This may be accomplished through a multiple dosing regimen or by employing a system that releases the medicament in a sustained fashion.

Attempts to sustain medication levels include the use of biodegradable materials, such as polymeric matrices, containing the medicament. The use of these matrices, for example, in the form of microparticles or microcarriers, can provide sustained release of medicaments by utilizing the inherent biodegradability of the polymer. The ability to provide a sustained level of medicament can result in improved patient compliance. For example, patient compliance can be particularly difficult in the treatment of affective disorders such as schizophrenia, depression, anxiety and in view of the large outpatient population and altered psychological state of the patient.

Certain methods of fabricating polymer-based sustained release devices comprise the steps of dissolving a polymer in a solvent, adding to the polymer solution the active agent to be incorporated and removing the solvent from the mixture, thereby forming a matrix of the polymer with the active agent distributed throughout the matrix. However, the physical characteristics of the microparticles, for example, the morphology, density and size, are significantly dependent upon all steps used in the method of preparation making control and tailoring of the physical characteristics of the resulting microparticles a difficult (sometimes impossible) and expensive undertaking.

For example, many sustained release compositions can exhibit an increased release of biologically active agent over the first twenty-four hours after administration, commonly referred to as a burst. In some instances, this burst can result in an undesirable increase in the levels of biologically active agent and/or minimal release of agent thereafter. Tailoring of the physical characteristics of the microparticles to provide an improved release can require modification of the entire process of preparation. Therefore, a need exists for methods of preparing sustained release microparticles where additional control over release kinetics by, for example, reducing the burst of agent and/or providing an improved release profile can be exerted.

SUMMARY OF THE INVENTION

The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent, also referred to herein as a "drug." The invention provides an improved process for the preparation of microparticles wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/drug matrix. That is, the method of the invention provides for the ability to decouple the fabrication of the polymer/drug

matrix from subsequent steps used to impart the desired physical characteristics to the injectable microparticles.

The method includes the steps of: (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/biologically active agent matrix can be provided by any suitable method.

In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, *e.g.*, a polymer solvent; and (b) removing the solvent, thereby forming the polymer/ biologically active agent matrix. The biologically active agent can be suspended (*e.g.*, completely or partially suspended) in the mixture and/or dissolved (*e.g.*, completely or partially dissolved) in the mixture.

As such, in one embodiment the invention relates to a method for preparing an injectable microparticle composition for the sustained release of a biologically active agent comprising the steps of: (a) preparing a mixture comprising a biologically active agent, a biocompatible polymer, and a solvent, thereby forming a single phase solvent system; (b) removing the solvent from the solution, thereby forming a polymer/biologically active agent matrix; (c) compressing the matrix using confined pressure compaction, thereby forming a compressed matrix; and (d) fragmenting the matrix, thereby forming the injectable microparticle composition.

In a preferred embodiment, compression of the polymer/biologically active agent matrix is conducted without the application of heat. For example, the compression is conducted at or below the transition temperature of the matrix. In one embodiment, the matrix is compressed at about ambient temperature (*e.g.*, room temperature such as about 15°C to about 30°C). In another embodiment, the matrix is compressed at or below room temperature. In one embodiment, fragmenting of the compressed matrix is conducted at or below the transition temperature of the polymer/biologically active agent matrix.

In a preferred embodiment, the biologically active agent is an antipsychotic drug such as aripiprazole, olanzapine or risperidone.

In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer, and a solvent, *e.g.*, a polymer solvent; (b) forming droplets of the mixture; (c) solidifying the droplets (*e.g.*, freezing), thereby forming solid droplets (*e.g.*, frozen droplets); and (d) extracting the solvent present in the solid droplets into a non-solvent, thereby forming the polymer/biologically active agent matrix.

The present invention also relates to sustained release microparticles that are formed by the methods described herein. The microparticles include a biocompatible polymer such as, for example, poly(lactic acid) or a poly(lactic acid-*co*-glycolic acid) copolymer, and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent such as a protein, peptide, nucleic acid or small organic molecule (*e.g.*, an antipsychotic agent).

In a particularly preferred embodiment, the microparticles prepared according the method of the invention include a biocompatible polymer and a drug used to treat affective disorders, such as schizophrenia, depression, and anxiety. Suitable drugs for treating affective disorders include, but are not limited to, risperidone, olanzapine and aripiprazole.

In one embodiment, the microparticles can further include one or more excipients and/or release modifiers. The particles can include one or more additional drugs.

Practice of the present invention can be used to prepare microparticles by using any suitable method of preparing the polymer/biologically active agent matrix followed by downstream tailoring of the physical characteristics of the resulting injectable microparticles. For example, the morphology and/or size of the initially fabricated polymer/biologically active agent matrix is decoupled from the physical characteristics of the resulting microparticles, which can impact the injectability and release profile of the microparticles.

For example, the present invention allows the production of dense microparticles for drug delivery. In one embodiment, the porosity of the polymer/drug matrix is reduced and thus a given volume of microparticles formed in accordance with the processes described herein contains a higher drug load than an

equivalent volume of polymer/biologically active agent matrix. Thus, practice of the present invention can be used to increase drug loads for a given dose volume.

Therefore, the improved method described herein provides for an efficient, facile and cost effective preparation of sustained release microparticles having desirable physical properties. For example, the microparticles prepared according to the methods described herein can exhibit a reduced initial release of biologically active agent, a higher sustained level of agent and/or a longer duration of release of the biologically active agent following administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of olanzapine concentration in blood plasma (nanograms/milliliter) versus time (days) for an *in vivo* study of three polymer/drug microparticle compositions (50 milligrams olanzapine/kilogram normalized dose) administered subcutaneously to Sprague-Dawley rats.

FIG. 2 is a plot of olanzapine concentration in blood plasma (nanograms/milliliter) versus time (days) for an *in vivo* study of two forms of a polymer/drug microparticle composition (50 milligrams olanzapine/kilogram normalized dose) administered subcutaneously to Sprague-Dawley rats. "Uncompacted" particles were produced by milling a cast film of a solution of polymer and drug. "Compacted" particles were further compacted and refragmented to produce injectable microparticles.

FIG. 3 is a bar chart showing the results of an 18 hour *in vitro* study demonstrating the effect of various solvents on the molecular weight of poly(*d,l*-lactide-*co*-glycolide) in the presence of olanzapine.

FIG. 4 is a plot showing the results of two *in vitro* studies measuring the cumulative release of insulin (as a percentage of total insulin) from three microparticle formulations in 0.1 M sodium phosphate, pH 7 at 37°C and one microparticle formulation in Hepes buffer, pH 7 at 37°C versus time (in days).

FIG. 5 is a plot of naltrexone concentration in blood plasma (nanograms/milliliter) versus time (days) for an *in vivo* study of four polymer/drug

microparticle compositions coated with various polymers and one uncoated control microparticle composition administered subcutaneously to Sprague-Dawley rats.

FIG. 6 is a plot of Bovine Serum Albumin (herein "BSA") concentration in blood plasma (nanograms/milliliter) versus time (days) for an *in vivo* study of three polymer/drug compositions (15 milligrams BSA/kilogram normalized dose) administered to rats.

DETAILED DESCRIPTION OF THE INVENTION

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent, also referred to herein as a "drug." The invention provides an improved process for the preparation of microparticles wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/biologically active agent matrix. That is, the method of the invention provides for the ability to decouple the fabrication of the polymer/biologically active agent matrix from subsequent steps used to impart the desired physical characteristics to the injectable microparticles.

The method includes the steps of: (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/biologically active agent matrix can be provided by any suitable method. A suitable method should not result in a significant reduction of the biological activity of the incorporated drug. As such, in embodiments wherein the drug is a labile agent, for example, a biologically active agent that can undergo degradation when exposed to heat or solvent, the polymer/biologically active agent matrix can be prepared at a

temperature which does not significantly reduce the biological activity of the drug. The method can further include the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix, referred to herein as "precompression fragmenting."

In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, *e.g.*, a polymer solvent; and (b) removing the solvent, thereby forming the polymer/ biologically active agent matrix. The biologically active agent can be suspended (*e.g.*, completely or partially suspended) in the mixture and/or dissolved (*e.g.*, completely or partially dissolved) in the mixture. For example, the solvent can be a solvent for both the biologically active agent and the biocompatible polymer, *e.g.*, both the biologically active agent and the polymer are dissolved in the solvent. In one embodiment, the mixture constitutes a single phase solvent system.

As such, in one embodiment the invention relates to a method for preparing an injectable microparticle composition for the sustained release of a biologically active agent comprising the steps of: (a) preparing a mixture comprising a biologically active agent, a biocompatible polymer, and a solvent, thereby forming a single phase solvent system; (b) removing the solvent from the solution, thereby forming a polymer/biologically active agent matrix; (c) compressing the matrix using confined pressure compaction, thereby forming a compressed matrix; and (d) fragmenting the matrix, thereby forming the injectable microparticle composition.

The term "single phase solvent system," as used herein, refers to a mixture that includes one or more liquids, *e.g.*, solvents, that are in a single phase and in which the polymer and biologically active agent are dissolved and/or suspended. When a combination of liquids is used, the liquids of the combination are miscible and when the liquids are mixed, a single phase, rather than separate phases, results. For example, when a combination of solvents is used, the solvents of the combination are miscible. A combination of liquids, *e.g.*, solvents, can be formed prior to, following, or simultaneously with the mixing of the polymer and/or agent with the solvent or solvents to form a single phase solvent system. In a preferred embodiment, the solvent used is a single solvent.

In a preferred embodiment, compressing the polymer/biologically active agent matrix is conducted without the application of heat. For example, the compression can be conducted at or below the transition temperature of the matrix. In one embodiment, the matrix is compressed at about ambient temperature or room temperature (*e.g.*, such as about 15°C to about 30°C). In one embodiment, fragmenting of the compressed matrix is conducted at or below the transition temperature of the polymer/biologically active agent matrix.

In a preferred embodiment, the biologically active agent is an antipsychotic drug such as aripiprazole, olanzapine or risperidone.

In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer, and a solvent, *e.g.*, a polymer solvent; (b) forming droplets of the mixture; (c) solidifying the droplets (*e.g.*, freezing), thereby forming solid droplets (*e.g.*, frozen droplets); and (d) extracting the solvent present in the solid droplets into a non-solvent, thereby forming the polymer/biologically active agent matrix. The matrix can then be filtered and dried.

The present invention also relates to the sustained release microparticles that are formed by the methods described herein. The microparticles include a biocompatible polymer such as, for example, poly(lactic acid) or a poly(lactic acid-*co*-glycolic acid) copolymer, and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent such as a protein, peptide, nucleic acid or small organic molecule. In a particularly preferred embodiment, the microparticles prepared according the method of the invention include a biocompatible polymer and a drug used to treat affective disorders, such as schizophrenia, depression, and anxiety. Suitable drugs for treating affective disorders include, but are not limited to, risperidone, olanzapine and aripiprazole.

In one embodiment, the microparticles can further include one or more excipients and/or release modifiers. The particles can include one or more additional drugs.

The invention also relates to use of the microparticles prepared according to the described method for the manufacture of a medicament for use in therapy. For

example, for use in treating affective disorders such as schizophrenia, depression and anxiety.

PREPARATION OF POLYMER/DRUG MATRIX

The terms "polymer/biologically active agent matrix" and "polymer/drug matrix," as used interchangeably herein, refer to a solid material comprising a biocompatible polymer (*e.g.*, a homopolymer, copolymer or polymer blend) and drug molecules, which are dispersed throughout the polymer. The polymer/biologically active agent matrix can be of any size and shape prior to compression and fragmenting. For example, the polymer/biologically active agent matrix can be a film, pellet, cylinder, disc or particle (*e.g.*, spherical, non-spherical or irregularly shaped). The polymer/drug matrix can be homogeneous or heterogeneous, for example, the polymer/drug matrix can have a homogeneous distribution of drug in the matrix or, alternatively, the distribution of drug in the matrix can be heterogeneous. The polymer/drug matrix can further comprise excipients such as, for example, surfactants, carbohydrates (*e.g.*, monosaccharides and polysaccharides), release modifying agents, stabilizers, one or more additional biologically active agents and any combination thereof.

Any suitable method can be used to provide the polymer/drug matrix for subsequent fragmentation and compression to form an injectable microparticle composition.

In one embodiment, the polymer/biologically active agent matrix is provided by (a) forming a mixture of a biologically active agent, a biocompatible polymer and a solvent, *e.g.*, a polymer solvent, and (b) removing the solvent, thereby forming a polymer/biologically active agent matrix. The biologically active agent can be in solution and/or suspended in the mixture. In one embodiment, the drug and polymer are dissolved and/or suspended in a single phase solvent system. A number of methods are known for providing the polymer/drug matrix in this manner.

For example, methods for forming a composition for the sustained release of biologically active agent are described in U.S. Patent No. 5,019,400, issued to Gombotz, *et al.*, on May 28, 1991; U.S. Patent No. 5,922,253 issued to Herbert, *et*

al., on July 13, 1999; and U.S. Patent No. 6,455,074 issued to Tracy, *et al.*, on September 24, 2002, the entire contents of each of which are incorporated herein by reference.

In this method, a mixture comprising a biologically active agent, a biocompatible polymer and a polymer solvent is processed to create droplets, wherein at least a significant portion of the droplets contains polymer, polymer solvent and the active agent. These droplets are then frozen by a suitable means. Examples of means for processing the mixture to form droplets include directing the dispersion through an ultrasonic nozzle, pressure nozzle, Rayleigh jet, or by other known means for creating droplets from a solution.

Means suitable for freezing droplets include directing the droplets into or near a liquified gas such as liquid argon or liquid nitrogen to form frozen microdroplets which are then separated from the liquified gas. The frozen microdroplets are then exposed to a liquid or solid non-solvent such as ethanol, hexane, ethanol mixed with hexane, heptane, ethanol mixed with heptane, pentane or oil.

The solvent in the frozen microdroplets is extracted as a solid and/or liquid into the non-solvent to form a polymer/active agent matrix comprising a biocompatible polymer and a biologically active agent. Mixing ethanol with other non-solvents, such as hexane, heptane or pentane, can increase the rate of solvent extraction, above that achieved by ethanol alone, from certain polymers such as, for example, poly(lactide-*co*-glycolide) polymers.

A wide range of sizes of polymer/drug matrices can be made by varying the droplet size, for example, by changing the ultrasonic nozzle diameter. If the polymer/drug matrix is in the form of particles and very large particles are desired, the particles can be extruded, for example, through a syringe directly into the cold liquid. Increasing the viscosity of the polymer solution can also increase the polymer/drug matrix (*e.g.*, particle) size. The size of the polymer/drug matrices (*e.g.*, particles) which can be produced by this process ranges, for example, from about 1 micrometer to greater than about 1000 micrometers in diameter.

Yet another method of forming a polymer/drug matrix from a suspension or solution comprising a biocompatible polymer and a biologically active agent includes film casting, such as in a mold, to form a film or a shape. For instance, after putting the suspension into a mold, the polymer solvent is then removed (*e.g.*, via evaporation or sublimation) or the temperature of the polymer suspension is reduced (*e.g.*, the polymer suspension is frozen) until a film or shape is obtained. Means for removing the solvent from a cast film are known in the art and include vacuum drying, lyophilization, flash drying, and sublimation, among others. The solvent is removed until the residual solvent levels are brought to concentrations that are suitable for administration to a patient. One of ordinary skill in the art can determine the concentrations of residual solvent in particles administered to a patient that are acceptable or tolerated without undue experimentation.

A further example of a process for the production of a polymer/drug matrix, *e.g.*, particles, is disclosed in U.S. Patent No. 3,737,337, incorporated by reference herein in its entirety, wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing mixture and, thereafter, the core material-containing mixture is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove solvent from the polymer/drug matrix, *e.g.*, particles.

Another example of a process in which solvent is removed from particles containing a substance is disclosed in U.S. Patent No. 3,523,906, incorporated herein by reference in its entirety. In this process, a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the particles is then accomplished by evaporation and the product is obtained.

In still another process, as shown in U.S. Patent No. 3,691,090, incorporated herein by reference in its entirety, organic solvent is evaporated from a dispersion of particles in an aqueous medium, preferably under reduced pressure.

Similarly, the disclosure of U.S. Patent No. 3,891,570, incorporated herein by reference in its entirety, shows a method in which solvent from a dispersion of particles in a polyhydric alcohol medium is evaporated from the particles by the application of heat or by subjecting the particles to reduced pressure.

Another example of a solvent removal process is shown in U.S. Patent No. 3,960,757, incorporated herein by reference in its entirety.

Tice *et al.*, in U.S. Patent No. 4,389,330, incorporated herein by reference in its entirety, describe the preparation of particles containing an active agent by a method including: (a) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material in that solvent; (b) dispersing the solvent containing the active agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming particles containing the active agent in the suspension; and (d) extracting the remainder of the solvent from the particles.

Solvent and/or solvent/nonsolvent systems suitable for production of a polymer/drug matrix can be determined via routine experimentation using techniques well known to those of ordinary skill in the art.

Suitable solvents for forming a poly(lactic acid-*co*-glycolic acid) polymer solution/drug mixture, for example, a dispersion of an agent in a polymer solution, or alternatively, a polymer/drug solution, *e.g.*, an agent co-dissolved with polymer as a single phase solvent system, include methylene chloride, acetone, ethyl acetate, methyl acetate, tetrahydrofuran, dimethylsulfoxide (DMSO), acetonitrile, and chloroform.

In another embodiment, the polymer/drug matrix can be provided by mixing one or more dry polymers with one or more dry biologically active agents. In yet another embodiment, the polymer/drug matrix may be supplied by purchasing the material from a commercial supplier.

As used herein, the terms "a" and "an" refer to one or more.

As used herein, the term "particle size" refers to a number median diameter as determined by conventional particle size measuring techniques known to those skilled in the art such as, for example, laser diffraction, photon correlation

spectroscopy, sedimentation field flow fractionation, disk centrifugation or electrical sensing zone method. Laser diffraction is preferred. The "number median diameter" reflects the distribution of particles (by number) as a function of particle diameter. An alternative designation of particle size often used in the art is the "volume median diameter." The volume median diameter is the median diameter of the volume weighted size distribution, also referred to as $D_{v,50}$. The volume median diameter reflects the distribution of volume as a function of particle diameter.

An "injectable microparticle," as defined herein, comprises a biocompatible polymer component having a volume median particle size from about 1 to about 1000 microns and having a biologically active agent dispersed therein. For example, the particle size can be about 500 microns or less, such as about 400, 300, 200 or about 100 microns or less. The microparticles can be of any shape, for example, spherical, non-spherical or irregular shape, and are suitable for administration by any means (*e.g.*, by needle, needle-free delivery, or inhalation). It is understood that injectable refers to a size range of the microparticle rather than the mode of administration employed to deliver the microparticles to a patient.

The term "release modifying agent," as used herein, refers to a material which, when incorporated into a polymer/drug matrix, modifies the drug-release characteristics of the matrix. A release modifying agent can, for example, either decrease or increase the rate of drug release from the matrix. One group of release modifying agents includes metal-containing salts, as disclosed in U.S. Patent No. 5,656,297 issued to Bernstein, *et al.*, on August 12, 1997, the contents of which are incorporated herein by reference.

"Sustained release," as that term is used herein, is release of biologically active agent from the injectable microparticles which occurs over a period which is longer than the period during which a biologically significant amount of agent would be available following direct administration of a solution of agent. In one embodiment, a sustained release is a release of agent which occurs over a period of at least about one day such as, for example, at least about 2, 4, 6, 8, 10, 15, 20, 30, 60, or at least about 90 days. A sustained release of agent can be a continuous or a discontinuous release, with relatively constant or varying rates of release. The

continuity of release and level of release can be affected by the type of polymer composition used (*e.g.*, monomer ratios, molecular weight, block composition, and varying combinations of polymers), protein loading, and/or selection of excipients to produce the desired effect.

"Sustained release" is also referred to in the art as "modified release," "prolonged release," "long acting release ('LAR')," or "extended release." "Sustained release," as used herein, also encompasses "sustained action" or "sustained effect." "Sustained action" and "sustained effect," as those terms are used herein, refer to an increase in the time period over which an agent performs its therapeutic, prophylactic or diagnostic activity as compared to an appropriate control. "Sustained action" is also known to those experienced in the art as "prolonged action" or "extended action."

The sustained release profile of the injectable microparticles prepared according to the method described herein can exhibit a reduced initial release of biologically active agent, a higher sustained level of agent and/or a longer duration of release of the agent following administration.

Without being bound by a particular theory, it is believed that the release of the biologically active agent can occur by two different mechanisms. First, the biologically active agent can be released by diffusion through aqueous liquid-filled channels generated in the polymer matrix, such as by the dissolution of the biologically active agent or by voids created by the removal of the polymer solvent during the preparation of the sustained release composition. A second mechanism is the release of the biologically active agent due to degradation of the polymer.

The rate of polymer and/or particle degradation can be controlled, in part, by changing polymer properties that influence the rate of hydration of the polymer. These properties include, for example, the ratio of lactide to glycolide; the isomeric form of the polymer, *e.g.*, the use of the L-isomer of a monomer instead of a racemic mixture; and the molecular weight of the polymer. These properties can affect hydrophilicity and crystallinity, which control the rate of hydration of the polymer.

By altering the properties of the polymer, the contributions of diffusion and/or polymer/particle degradation to biologically active agent release can be

controlled. For example, increasing the glycolide content of a poly(lactide-*co*-glycolide) polymer and decreasing the molecular weight of the polymer can enhance the hydrolysis of the polymer and thus can provide an increased biologically active agent release from polymer erosion. Without being held to any particular theory, it is believed that the morphology and/or density of the polymer matrix can also effect the diffusion of an agent from the microparticles and/or the degradation of the microparticle or its constituent polymer.

Polymers which can be used in the formulation of polymer/drug matrix microparticles include any polymer which is biocompatible. Biocompatible polymers suitable for use in the present invention include biodegradable and non-biodegradable polymers and blends and copolymers thereof, as described herein. A polymer is biocompatible if the polymer and any degradation products of the polymer are non-toxic to the recipient and also possess no significant deleterious or untoward effects on the recipient's body, such as a significant immunological reaction at the injection site.

"Biodegradable," as defined herein, means the composition will degrade or erode *in vivo* to form smaller chemical species. Degradation can result, for example, by enzymatic, chemical and physical processes. Suitable biocompatible, biodegradable polymers include, for example, poly(lactides), poly(glycolides), poly(lactide-*co*-glycolides), poly(lactic acid)s, poly(glycolic acid)s, polycarbonates, polyesteramides, polyanydrides, poly(amino acids), polyorthoesters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers or polyethylene glycol and polyorthoester, biodegradable polyurethane, blends thereof, and copolymers thereof.

Suitable biocompatible, non-biodegradable polymers include non-biodegradable polymers such as, for example, polyacrylates, polymers of ethylene-vinyl acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinylchloride, polyvinyl flouride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, blends thereof, and copolymers thereof, such as PLG-*co*-EMPO described in copending U.S. Patent Application No. 09/886,394 entitled "Functionalized Degradable Polymer" and filed on June 22, 2001, the entire contents of which is hereby incorporated by reference.

Further, the terminal functionalities or pendant groups of the polymers can be modified, for example, to modify hydrophobicity, hydrophilicity and/or to provide, remove or block moieties which can interact with the active agent via, for example, ionic or hydrogen bonding.

In a preferred embodiment of the present invention, the polymer used to produce the particles is a poly(lactic acid-*co*-glycolic acid) ("PLG") copolymer. The poly(lactic acid-*co*-glycolic acid) polymer includes *d*-, *l*-, or racemic forms of the polymer, for example, in some embodiments the polymer used is poly(*d,l*-lactic acid-*co*-glycolic acid). In some embodiments, the poly(lactic acid-*co*-glycolic acid) contains free carboxyl end groups. In other embodiments, the poly(lactic acid-*co*-glycolic acid) contains alkyl ester end groups such as methyl ester end groups.

Acceptable molecular weights for polymers used in this invention can be determined by a person of ordinary skill in the art taking into consideration factors such as the desired polymer degradation rate, physical properties such as mechanical strength, and rate of dissolution of polymer in solvent. Typically, an acceptable range of molecular weight is of about 2,000 Daltons to about 2,000,000 Daltons. In a preferred embodiment, the polymer is a biodegradable polymer or copolymer. In a more preferred embodiment, the polymer is a poly(lactide-*co*-glycolide) which can have a lactide:glycolide ratio of about 25:75 to about 85:15, *e.g.*, about 25:75, about 50:50, about 75:25, or about 85:15, and a molecular weight of about 5,000 Daltons to about 150,000 Daltons. In an even more preferred embodiment, the molecular weight of the PLG used in the present invention has a molecular weight of about 5,000 Daltons to about 42,000 Daltons.

The term "biologically active agent," as used herein, is an agent or its pharmaceutically acceptable salt which, when released *in vivo*, possesses the desired biological activity, for example, therapeutic, diagnostic and/or prophylactic properties *in vivo*. It is understood that the term includes stabilized biologically active agents as described herein. The terms "biologically active agent," "therapeutic, prophylactic or diagnostic agent," "drug," "active agent," and "agent"

are used interchangeably herein. Preferably, the drug is soluble in the solvent or combination of solvents that also dissolve the polymer.

Examples of suitable biologically active agents include, but are not limited to, antipsychotic agents such as aripiprazole, risperidone, and olanzapine; antitumor agents such as bleomycin hydrochloride, carboplatin, methotrexate and adriamycin; antibiotics such as gentamicin, tetracycline hydrochloride and ampicillin; antipyretic, analgesic and anti-inflammatory 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 sodium 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; and narcotic antagonists such as nalorphine hydrochloride.

Additional biologically active agents suitable for use in the invention include, but are not limited to, proteins, muteins and active fragments thereof, such as immunoglobulins, antibodies, cytokines (*e.g.*, lymphokines, monokines, chemokines), interleukins, interferons (β-IFN, α-IFN and γ-IFN), erythropoietin, nucleases, tumor necrosis factor, colony stimulating factors, 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), antigens, blood coagulation factors; growth

factors; peptides such as protein inhibitors, protein antagonists, and protein agonists; nucleic acids, such as antisense molecules; oligonucleotides; and ribozymes.

In a particular embodiment, the biologically active agent is a labile drug. As used herein, "labile drug" refers to a drug which loses a substantial amount of activity when either warmed to elevated temperatures, such as temperatures greater than physiological temperatures (*e.g.*, about 37°C), or dissolved in an organic solvent or in solution at an aqueous/organic interface. Examples of labile drugs can include proteins, peptides and nucleic acids. By decoupling the process of forming the polymer/drug matrix from the final product morphology, the present processes enable formation of the polymer/drug matrix using variety of matrix formation techniques such as those that employ low temperatures, *e.g.*, room temperature or below, while still producing injectable microparticles for sustained release of the labile agent. In addition, the instant processes enable the formation of the polymer/drug matrix using various solvent systems such as, for example, forming the matrix without mixing the drug with an organic solvent.

The microparticles prepared according to the invention can contain from about 0.01% (w/w) to about 90% (w/w) of the biologically active agent (dry weight of composition). The amount of agent can vary depending upon the desired effect of the agent, the planned release levels, and the time span over which the agent is to be released. A preferred range of agent loading is about 0.1% (w/w) to about 75% (w/w), for example, about 0.1% (w/w) to about 60% (w/w). A more preferred range of agent loading is about 0.5% (w/w) to about 75% (w/w) agent, for example, about 0.5% (w/w) to about 60% (w/w).

In one embodiment, the biologically active agent is stabilized. The biologically active agent can be stabilized against degradation, loss of potency and/or loss of biological activity, all of which can occur during formation of the sustained release composition having the biologically active agent dispersed therein, and/or prior to and during *in vivo* release of the biologically active agent. In one embodiment, stabilization can result in a decrease in the solubility of the biologically active agent, the consequence of which is a reduction in the initial release of biologically active agent, in particular, when release is from a sustained release

composition. In addition, the period of release of the biologically active agent can be prolonged.

Stabilization of the biologically active agent can be accomplished, for example, by the use of a stabilizing agent or a specific combination of stabilizing agents. The stabilizing agent can be present in the mixture. "Stabilizing agent," as that term is used herein, is any agent which binds or interacts in a covalent or non-covalent manner or is included with the biologically active agent. Stabilizing agents suitable for use in the invention are described in U.S. Patent Nos. 5,716,644 and 5,674,534 to Zale, *et al.*; U.S. Patent Nos. 5,654,010 and 5,667,808 to Johnson, *et al.*; U.S. Patent Nos. 5,711,968 to Tracy, *et al.*, and 6,265,389 to Burke, *et al.*; and in copending U.S. Patent Application 08/934,830 by Burke, *et al.*, filed on September 22, 1997, the entire teachings of each of which are incorporated herein by reference.

For example, a metal cation can be complexed with the biologically active agent, or the biologically active agent can be complexed with a polycationic complexing agent such as protamine, albumin, spermidine and spermine, or associated with a "salting-out" salt. In addition, a specific combination of stabilizing agents and/or excipients may be needed to optimize stabilization of the biologically active agent. For example, when the biologically active agent in the mixture is an acid-stable or free sulfhydryl-containing protein such as β-IFN, a particular combination of stabilizing agents which includes a disaccharide and an acidic excipient can be added to the mixture. This type of stabilizing formulation is described in detail in U.S. Patent No. 6,465,425 issued to Tracy, *et al.*, on October 15, 2002, the entire contents of which is incorporated herein by reference.

Suitable metal cations include any metal cation capable of complexing with the biologically active agent. A metal cation-stabilized biologically active agent, as defined herein, comprises a biologically active agent and at least one type of metal cation wherein the cation is not significantly oxidizing to the biologically active agent. In a particular embodiment, the metal cation is multivalent, for example, having a valency of +2 or more. If the agent is metal cation-stabilized, it is preferred that the metal cation is complexed to the biologically active agent.

Suitable stabilizing metal cations include biocompatible metal cations. A metal cation is biocompatible if the cation is non-toxic to the recipient in the quantities used and also presents no significant deleterious or untoward effects on the recipient's body such as a significant immunological reaction at the injection site. The suitability of metal cations for stabilizing biologically active agents and the ratio of metal cation to biologically active agent needed can be determined by one of ordinary skill in the art by performing a variety of stability indicating techniques such as polyacrylamide gel electrophoresis, isoelectric focusing, reverse phase chromatography, and High Performance Liquid Chromatography (HPLC) analysis on particles of metal cation-stabilized biologically active agents prior to and following particle size reduction and/or encapsulation. The molar ratio of metal cation to biologically active agent is typically between about 1:2 and about 100:1, preferably between about 2:1 and about 12:1.

Examples of stabilizing metal cations include, but are not limited to, K^+, Zn^{+2}, Mg^{+2} and Ca^{+2}. Stabilizing metal cations also include cations of transition metals such as Cu^{+2}. Combinations of metal cations can also be employed. For example, in one embodiment, Zn^{+2} is used as a stabilizing metal cation for bovine serum albumin (herein "BSA") at a zinc cation component to BSA molar ratio of about 4:1 to about 100:1. In a preferred embodiment, the zinc cation component to BSA molar ratio is about 4:1 to about 12:1, and most preferably 10:1.

The biologically active agent can also be stabilized with at least one polycationic complexing agent. Suitable polycationic complexing agents include, but are not limited to, protamine, spermine, spermidine and albumin. The suitability of polycationic complexing agents for stabilizing biologically active agents can be determined by one of ordinary skill in the art in the manner described above for stabilization with a metal cation. An equal weight ratio of polycationic complexing agent to biologically active agent is suitable.

Further, excipients can be added to the compositions of the present invention such as, for example, to maintain the potency of the biologically active agent over the duration of release and to modify polymer degradation. One or more excipients can be added to the mixture which is then used to form the polymer/biologically

active agent matrix. For example, an excipient may be suspended or dissolved along with polymer and agent in a solvent system prior to formation of the polymer drug matrix. Alternatively, excipient(s) can be mixed with the polymer/biologically active agent matrix from which the solvent has been removed either prior to or following fragmentation and/or compression of the matrix. For example, an excipient can be blended with the compressed and fragmented injectable microparticle composition.

Suitable excipients include, for example, carbohydrates, amino acids, fatty acids, surfactants, and bulking agents. Such excipients are known to those of ordinary skill in the art. An acidic or a basic excipient is also suitable. The amount of excipient used is based on its ratio to the biologically active agent, on a weight basis. For amino acids, fatty acids and carbohydrates, such as sucrose, trehalose, lactose, mannitol, dextran and heparin, the ratio of carbohydrate to biologically active agent, is typically between about 1:10 and about 20:1. For surfactants, the ratio of surfactant to biologically active agent is typically between about 1:1000 and about 2:1. Bulking agents typically comprise inert materials. Suitable bulking agents are known to those of ordinary skill in the art.

The excipient can comprise a metal cation component which is separately dispersed within the polymer matrix. This metal cation component acts to modulate the release of the biologically active agent and is not complexed with the biologically active agent. The metal cation component can optionally contain the same species of metal cation, as is contained in the metal cation stabilized biologically active agent, if present, and/or can contain one or more different species of metal cation. The metal cation component acts to modulate the release of the biologically active agent from the polymer matrix of the sustained release composition and can enhance the stability of the biologically active agent in the composition. A metal cation component used in modulating release typically comprises at least one type of multivalent metal cation. Examples of metal cation components suitable to modulate release include or contain, for example, $Mg(OH)_2$, $MgCO_3$ (such as $4MgCO_3.Mg(OH)_2.5H_2O$), $MgSO_4$, $Zn(OAc)_2$, $Mg(OAc)_2$, $ZnCO_3$ (such as $3Zn(OH)_2{\cdot}2ZnCO_3)ZnSO_4$, $ZnCl_2$, $MgCl_2$, $CaCO_3$, $Zn_3(C_6H_5O_7)_2$ and

$Mg_3(C_6H_5O_7)_2$. A suitable ratio of metal cation component to polymer is between about 1:99 to about 1:2 by weight. The optimum ratio depends upon the polymer and the metal cation component utilized and can be determined by one of ordinary skill in the art without undue experimentation. A polymer matrix containing a dispersed metal cation component to modulate the release of a biologically active agent from the polymer matrix is further described in U.S. Patent Nos. 5,656,297 issued to Bernstein, *et al.*, on August 12, 1997, and 5,912,015 issued to Bernstein, *et al.*, on June 15, 1999, the entire contents of both of which are incorporated herein by reference. In yet another embodiment, at least one pore forming agent, such as a water soluble salt, sugar or amino acid, is included in the sustained release composition to modify the microstructure of the particles. The proportion of pore forming agent added to the mixture, *e.g.*, a dispersion or solution, comprising a biologically active agent, a biocompatible polymer, and a polymer solvent is between about 0.1% (w/w) to about 30% (w/w).

COMPRESSION

The polymer/drug matrix can be compressed using any suitable method. For example, the polymer/drug matrix can be compressed using confined pressure compaction, *e.g.*, molding, tableting, and roll pressing, or by extrusion, *e.g.*, pellet milling and screw extrusion. Preferably, the polymer/drug matrix is compressed using confined pressure compaction.

The term "confined pressure compaction," as used herein, refers to compaction of a material using a confined pressure device such as, for example, a device in which internal motion and shear of the polymer/drug matrix is incidental to consolidation of the matrix in a closed mold or between two surfaces. Preferably, the confined pressure compaction is conducted without the application of heat, *e.g.*, the application of heat other than the heat generated by the act of compressing the matrix. For example, the compression of the matrix is conducted at ambient temperature. For example, compression of the matrix is conducted at about room temperature such as about 15°C to about 30°C, about 17°C to about 28°C, about 20°C

to about 25°C, or about 21°C to about 22°C. In another embodiment, the matrix is compressed at or below room temperature.

Suitable equipment for compressing the polymer/drug matrix includes, but is not limited to, die and press systems, roll presses, and tableting presses. For example, hydraulic presses such as those produced by Carver, Inc. (Wabash, IN) can be used in conjunction with a die. In one embodiment, a Carver Model C Press is used. The die is of any shape or size that permits the formation of a compressed polymer/drug matrix having the desired physical characteristics (*e.g.*, density and morphology). In one embodiment, a Carver Model C Press is used in conjunction with 1/4 inch to ½ inch diameter cylindrical dies to compress the polymer/drug matrix.

FRAGMENTATION

The polymer/drug matrix can be fragmented following compression or both prior to and following compression using any suitable method. Suitable fragmentation methods include, but are not limited to, grinding, shearing, shocking, shattering, granulating, pulverizing, shredding, crushing, and/or milling. Suitable equipment for fragmenting the polymer/drug matrix includes, but is not limited to, crushers, impact mills (*e.g.*, hammer mills, impact breakers), roll crushers, roller mills, pin mills, tumbling mills, centrifugal mills, and fluid-energy mills (*e.g.*, jet mills), among others that are well known to one of ordinary skill in the art. An example of a suitable mill for fragmenting the polymer/drug matrix is the 24-tooth Ultra Centrifugal Mill made by Retsch, Inc. (Newtown, PA). Another example is the Fluid Air Granumill Jr. (Fluid Air, Inc., Aurora, IL).

In one embodiment, multiple stage fragmentation is used to fragment the polymer/drug matrix, for example, two or more pieces of fragmentation equipment are used to produce particles having desired physical characteristics. A particle size classifier (*e.g.*, an appropriately sized sieve) can be used in conjunction with the fragmentation apparatus to separate particles by size.

Fragmentation of the polymer/drug matrix can be performed under various conditions of temperature, for example, cooling or cryogenic cooling can be employed to reduce the temperature of the polymer/drug matrix during processing.

In a preferred embodiment, the temperature of the polymer/drug matrix is kept at or below the transition temperature of the polymer/drug matrix, *e.g.*, below the phase transition temperature or below the glass transition temperature of the polymer/drug matrix. In another preferred embodiment, the temperature of the polymer/drug matrix is kept below any temperature at which the agent would be subject to substantial degradation of its therapeutic, prophylactic or diagnostic effect.

In a specific embodiment, the polymer/drug matrix is also fragmented prior to the step of compressing the matrix (referred to herein as "precompression fragmenting"). Precompression fragmenting of the polymer/drug matrix can facilitate transfer of the polymer/drug matrix to a compression apparatus. For example, a film, block, or particles comprising the polymer/drug matrix is fragmented to form a flowable powder to facilitate transfer of the material to a suitable compression apparatus.

The compression and fragmenting steps can be conducted multiple times. In one embodiment, the compressed matrix is fragmented and then again compressed. The recompressed matrix is further fragmented and compressed as necessary to achieve a compressed polymer/drug matrix having a desired density and/or morphology. The resulting compressed polymer/drug matrix is then fragmented to produce the injectable microparticle composition product.

The size range of the injectable microparticles prepared by the present method can be controlled in the fragmentation step. For example, the final particle size distribution is typically a function of the total grinding or milling time, with shorter times producing, on average, larger particles and with longer grinding or milling times producing, on average, smaller particles. The size range of a sample of microparticles produced in this way can be further restricted by sorting, for example, sieving, thus achieving particles within a specified size range.

The injectable microparticles prepared according to the method described herein can be further modified to achieve a desired sustained release profile of the

biologically active agent. In one embodiment, a substantial portion of the exterior surface of the injectable microparticles can be annealed or coated. Annealing is accomplished, for example, by the application of heat or an annealing solvent, wherein the annealing solvent is a solvent for the polymer of the injectable microparticle. The application of heat or an annealing solvent can be performed, for example, by using a fluidized bed system such as the Wurster process. Coating can be conducted using a suitable coating apparatus using a polymer or combination of polymers which can be the same or different from the polymer of the unmodified matrix.

"Annealing," as that term is used herein, refers to treating a substantial portion of the exterior surface of the injectable microparticles by the application of an external stress which increases the fluidity of the surface of the microparticles and upon rehardening results in a smoother and less porous outer layer.

Thus, in one embodiment, the sustained release composition of the invention comprises injectable microparticles comprising a biocompatible polymer and a biologically active agent and characterized by a porous center and a less porous outer layer, wherein the outer layer and the center consist of essentially the same materials, *e.g.*, other components can be present either in the center or outer layer provided that the component does not function as a coating material. The variance in porosity can be achieved by annealing at least a substantial portion of the exterior surface of a solid polymer/active agent matrix. A process for annealing the surface of a sustained release composition comprising a polymer and an active agent is disclosed in U.S. Patent No. 6,479,065 issued to Jaworowicz, *et al.*, on November 12, 2002, incorporated herein by reference in its entirety.

The present invention also includes microparticles produced according to the methods described herein. In addition, the invention is directed to pharmaceutical compositions comprising the microparticles. Pharmaceutical compositions comprising microparticles are suitable for administration to a patient. The pharmaceutical compositions described herein may also comprise pharmaceutically acceptable excipients such as, for example, diluents, stabilizers, and delivery vehicles. Pharmaceutically acceptable excipients can be selected by one of ordinary

skill in the art without undue experimentation. Compositions for the delivery of microparticles are described, for example, in U.S. Patent No, 6,495,164 issued to Ramstack, *et al.*, on December 17, 2002.

The composition of this invention can be administered *in vivo*, for example, to a human or to an animal, orally, or parenterally such as by injection, implantation (*e.g.*, subcutaneously, intramuscularly, intraperitoneally, intracranially, and intradermally), administration to mucosal membranes (*e.g.*, intranasally, intravaginally, intrapulmonary, buccally or by means of a suppository), or *in situ* delivery (*e.g.*, by enema or aerosol spray) to provide the desired dosage of biologically active agent based on the known parameters for treatment with the particular agent of the various medical conditions.

The sustained release composition can be administered using any dosing schedule which achieves the desired therapeutic levels for the desired period of time. For example, the sustained release composition can be administered and the patient monitored until levels of the drug being delivered return to baseline. Following a return to baseline, the sustained release composition can be administered again. Alternatively, the subsequent administration of the sustained release composition can occur prior to achieving baseline levels in the patient.

The injectable microparticles of the present invention are used in a method for providing a therapeutically, prophylactically, or diagnostically effective amount of a biologically active agent to a subject for a sustained period. The injectable microparticle compositions described herein provide increased therapeutic benefits by reducing fluctuations in active agent concentration in blood, by providing a more desirable release profile and by potentially lowering the total amount of biologically active agent needed to provide a therapeutic benefit without the need for additional components in the composition.

As used herein, a "therapeutically effective amount," "prophylactically effective amount" or "diagnostically effective amount" is the amount of the biologically active agent or of the sustained release composition of biologically active agent needed to elicit the desired biological, prophylactic or diagnostic response following administration. For example, the desired response can be a

reduction (complete or partial) of symptoms associated with affective disorders, such as, schizophrenia, depression and/or anxiety.

The present invention also includes microparticles produced according to the methods described herein. The invention is also directed to pharmaceutical compositions comprising the microparticles. Pharmaceutical compositions comprising microparticles are suitable for administration to a patient. The pharmaceutical compositions described herein may also comprise pharmaceutically acceptable excipients such as, for example, diluents, stabilizers, and delivery vehicles. Pharmaceutically acceptable excipients can be selected by one of ordinary skill in the art without undue experimentation.

EXEMPLIFICATION

The invention will now be further and specifically described by the following examples which are not intended to be limiting.

EXAMPLE 1

Injectable microparticles comprising polymer and olanzapine were prepared using an efficient and facile single solvent process. PLG polymer and olanzapine were co-dissolved in a single solvent; (2) the solvent was removed by vacuum drying or sublimation to form a polymer/drug matrix; (3) the matrix was milled to produce a powder; (4) the resulting powder was compacted to form a compressed matrix; and (5) the compressed matrix was milled to form a dense, injectable microparticle formulation.

Specifically, an injectable microparticle composition comprising olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine) and poly(*d,l*-lactide-*co*-glycolide) polymer (herein referred to generically as "PLG") was prepared by co-dissolving olanzapine (Dr. Reddy's Laboratories, Ltd., Upper Saddle River, NJ) and PLG in methylene chloride. The olanzapine loading was about 30% (w/w) of the final weight of the microparticle composition. However, it is understood that other solvents, for example, acetone, dimethylsulfoxide (DMSO), acetonitrile, and ethyl acetate are suitable for use. Table I shows specific

polymer/olanzapine mixtures that were produced and which were processed into microparticles as described below.

Table I: Olanzapine/polymer/solvent mixtures

Formulation	Target Olanzapine Load	PLG Polymer Type [Lactide:Glycolide Ratio; Intrinsic Viscosity; End Group]	Solvent
A	30% (w/w)	50:50, 0.75 dL/g; Acid end group	CH_2Cl_2
B	30% (w/w)	75:25; 0.60 dL/g; Lauryl ester end group	CH_2Cl_2
C	30% (w/w)	50:50; 0.61 dL/g; Lauryl ester end group	CH_2Cl_2

The olanzapine/polymer/solvent mixtures were poured into either a polytetrafluoroethylene flat mold (approximately 1 inch x 1 inch x ½ inch deep) or a 3 inch diameter jar to form a film. The films were then dried either in an FTS Dura-Dry Lyophilizer (Kinetic Systems, Inc., Santa Clara, CA) or in a vacuum oven. Films were dried under various conditions including variation of vacuum, pressure, temperature, and drying time.

The films were milled using a 24-tooth Retsch Ultra Centrifugal Mill (Retsch, Inc., Newtown, PA) operating at 14,000 rpm. The collection pan was filled with liquid nitrogen prior to milling. The resulting powder, collected from the collection pan, was a flowable product that aided subsequent compaction steps.

A portion of the powders produced by milling the films were retained for analysis at this point. These powders were retained for comparison with the powders made by the subsequent compacting and re-milling of the film powders described below.

A portion of the milled powders was compacted using a Carver Model C Press (Carver, Inc., Wabash, IN) and either about 1/4 inch or about ½ inch cylindrical dies. About 50 to about 300 milligrams of milled powder was filled into the dies and compacted at a machine setting of about 5000 pounds for about 30 seconds at room temperature to form pellets.

The compacted matrix was subsequently milled using a 24-tooth Retsch Ultra Centrifugal Mill (Retsch, Inc., Newtown, PA) operating at 14,000 rpm. The collection pan was filled with liquid nitrogen prior to milling. The final powder was collected from the collection pan and placed into vials for analysis.

The activity of olanzapine can be assessed based on interaction with three significant neurotransmitter receptor subtypes: the D_2 class of dopamine receptors; the $5HT_{2A}$ subtype of serotonin receptors; and the M_1 subtype of muscarinic receptors. Olanzapine activity was assessed both before and after incorporation into the matrix using suitable radioligand assays.

Specifically, competition radioligand binding assays for the D_2, $5HT_{2A}$ and M_1 receptors were performed using [^{3}H]raclopride, [^{3}H]ketanserin and [^{3}H]pirenzepine, respectively. Stock solutions of native olanzapine (10 mM) and olanzapine extracted from Formulation A (Table I) microparticles (10 mM, based on % olanzapine load) were made in ethanol. Subsequent dilutions were made into 50 mM Tris HCl, pH 7.4. Binding assays varied according to the receptor/radioligand combination investigated. All assays were done with the total and non-specific binding determined in triplicate with three different receptor preparations on three separate occasions. Table II shows K_i values (the concentration of competing ligand in a comparison assay which would occupy 50% of the receptors if no radioligand were present) for radioligand displacement by native olanzapine and olanzapine contained within microparticles formed from Formulation A as shown in Table I.

Table II: K_i values for radioligand displacement by native olanzapine and olanzapine contained within microparticles

Radioligand (Receptor)	**K_i Native Olanzapine**	**K_i Olanzapine in Formulation A Microparticles**
[^{3}H]raclopride (D_2)	13.6 ± 0.68 nM	11.5 ± 4.3 nM
[^{3}H]ketanserin (M_1)	12.8 ± 2.9 nM	14.9 ± 1.2 nM
[^{3}H]pirenzepine ($5HT_{2A}$)	1.32 ± 0.21 nM	1.55 ± 0.32 nM

There was no significant difference between the inhibition constants of native olanzapine and olanzapine extracted from the Formulation A microparticles in terms of their potencies in displacing radioligands from D_2, M_1 and $5HT_{2A}$ receptors.

EXAMPLE 2

In vivo studies were preformed to evaluate the pharmacokinetic profile of olanzapine in rats following administration of a single subcutaneous dose of formulated olanzapine as prepared in Example 1.

Male Sprague-Dawley rats (450 ± 50 grams) were obtained from Charles River Laboratories, Inc. (Wilmington, MA). Animals were divided into four test groups. Groups 1-3 received the injectable microparticles prepared according to Example 1 and detailed in Table 1 as resulting Formulations A, B and C. Group 1 was injected subcutaneously once with nominal 83 milligrams of particles produced from Formulation A. Group 2 was injected subcutaneously once with nominal 83 milligrams of particles produced from Formulation B. Group 3 was injected subcutaneously once with nominal 83 milligrams of particles produced from Formulation C. Group 4 was injected subcutaneously once with 5 milligrams of bulk olanzapine.

Specifically, animals were injected subcutaneously into the interscapular region. The injection vehicle was 3% carboxymethylcellulose ('CMC') (low viscosity) and 0.1% TWEEN® 20 (*i.e.*, polyoxyethylene 20 sorbitan monooleate, TWEEN® is a trademark of ICI Americas, Inc.) in 0.9% aqueous sodium chloride. Each animal of Groups 1-3 received a dose comprising approximately 83 milligrams of microparticles containing about 25 milligrams of olanzapine (30% drug load) in a vehicle volume of 0.75 milliliters.

Blood samples were collected via a lateral tail vein after anesthesia with halothane. Blood samples were collected at 2, 4, 8, and 24 hours and then at 2, 4, 7, 10, 14, 17, 21, 24, and 28 days after injection. The blood was transferred to tubes containing K_2 EDTA and mixing beads and processed to separate the plasma. Olanzapine was detected in rat plasma using a procedure involving the analysis of an

acetonitrile precipitated extract of rat plasma by high performance liquid chromatography coupled with PE/Sciex API 2000 mass spectrometer using positive ion electron spray ionization and multiple reaction monitoring mode.

Two weeks of measurable olanzapine levels were detected *in vivo*. FIG. 1 shows olanzapine plasma concentration versus time for a normalized dose of 50 milligrams/kilogram for microparticles produced using Formulations A, B and C. This study demonstrates that microparticles comprising olanzapine and polymer produced as described above are capable of a release of olanzapine of at least about 2 weeks *in vivo*.

An additional *in vivo* study was conducted to investigate the effects of compaction and refragmentation of injectable microparticles. The study was conducted substantially as described above. FIG. 2 shows olanzapine plasma concentration versus time for a normalized dose of 50 milligrams/kilogram for two forms of particles produced using Formulation B. The figure compares the olanzapine plasma release from particles produced by milling the cast film as in Example 1 (shown in FIG. 2 as "uncompacted") with the release resulting from particles that were further compacted and refragmented as in Example 1 (shown in FIG. 2 as "compacted"). The data points shown in FIG. 2 represent all of the timepoints at which measurable levels of olanzapine could be detected in the blood plasma. FIG. 2 shows that a higher burst and a longer duration of release resulted from administration of the compacted and refragmented material versus that resulting from administration of the uncompacted material.

EXAMPLE 3

The molecular weight of the polymer in the microparticles prepared in Example 1 was determined by gel permeation chromatography (GPC). The analysis was completed using a Waters Alliance 2695 high performance liquid chromatograph using a differential refractometer.

Samples of olanzapine-containing injectable microparticles were collected and kept refrigerated at 2-8°C for one week prior to analysis. The residual solvent levels in the microparticle samples was about 3% by weight. The samples were

assayed by GPC and found to have a significantly lower molecular weight (MW) than the starting bulk polymer. For example, the polymer of Formulation B showed a 46% decrease in average molecular weight and the polymer of Formulation C showed a 28% decrease in average molecular weight.

In view of the loss of polymer molecular weight for the microparticles produced according to Example 1, further experiments were conducted to test the effect of solvent choice on polymer degradation. It was found that among the solvents tested (methylene chloride, ethyl acetate, acetone and DMSO), a loss of polymer molecular weight was found only when methylene chloride was used as a solvent.

The effect was tested by preparing a solution containing 10% by weight polymer and 3% by weight olanzapine in a variety of solvents, taking a sample for gel permeation chromatography (GPC) assay immediately, and then taking another sample after 18 hours at room temperature. FIG. 3 shows a graph of the resulting polymer molecular weight (MW), in kilodaltons (kD), for each sample. The results demonstrate that the polymer degradation is most significant when methylene chloride is the processing solvent. Without wishing to be held to any particular theory, it is believed that the mechanism of action is a solvent-mediated nucleophilic attack of the ester linkages in the polymer by the tertiary amine group of the olanzapine. By using other solvents such as DMSO or ethyl acetate, the drug-catalyzed polymer degradation can be reduced. Such effects are described in U.S. Patent No. 6,379,704, issued on April 30, 2002, entitled, "Method For Preparing Microparticles Having a Selected Polymer Molecular Weight" to Wright, *et al.*

Microparticles comprising the polymer and olanzapine loading shown in Table 1 but using dimethylsulfoxide (DMSO) in place of methylene chloride were formed as described in Example 1. These microparticles were tested *in vivo* as described in Example 2.

EXAMPLE 4

This example describes the production of microparticles comprising insulin and poly(lactide-*co*-glycolide) polymers and subsequent *in vitro* studies of insulin release from the microparticles.

Insulin powders were formulated using bulk insulin powder (99.4% insulin, 0.4% zinc and 0.2% impurities) (Diosynth, Inc., Des Plaines, IL). The bulk insulin powder was mixed in a buffer system (*e.g.*, phosphate buffer, carbonate buffer, 1% acetic acid, or 0.1% hydrochloric acid) and zinc acetate was added to give a desired zinc to insulin molar ratio (*e.g.*, 2:1, 10:1 or 30:1 zinc:insulin). The resulting mixture was then spray freeze dried to give an insulin powder.

For example, two insulin powders were produced. Insulin Powder Formulation I was prepared by mixing bulk insulin powder in 1% acetic acid at 10 milligrams insulin/milliliter and spray freeze drying the mixture. Insulin Powder Formulation II was prepared by mixing bulk insulin powder in 10mM sodium bicarbonate ($NaHCO_3$) at 20 milligrams insulin/milliliter and spray freeze drying the resulting mixture. Both mixtures were spray freeze dried by combining the mixture with a nitrogen gas stream produced from a liquid nitrogen stream at 15 psi and atomizing the resulting stream at 115 psi into a tank of liquid nitrogen using a Spray Systems, Inc. Model #205070 Spray Nozzle (Wheaton, IL).

A mixture of about 5-30% (w/w) insulin powder was made using about 10 to 30% (w/w) polymer dissolved in methylene chloride. Polymers that were used included poly(d,l-lactide-*co*-glycolide) polymers having 50 mol% d,l-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 2A polymer, MEDISORB® 5050 DL PLG 2.5A polymer, and MEDISORB® 5050 DL PLG 3.5A polymer, available from Alkermes, Inc., Cincinnati, OH) and PLG-*co*-EMPO (a functionalized PLG characterized by 8% *l*-lactide, 19% glycolide and 13% ethyl-2-methyl-4-pentenoate oxide (EMPO)). Some mixtures also included PLURONIC® F68 (a trademark of BASF Corp., Mount Olive, NJ), a difunctional ethylene oxide/propylene oxide block copolymer surfactant terminating in primary hydroxyl groups. Table III shows four formulations of mixtures from which microparticles were prepared.

Table III: Insulin Mixture Formulations

Formulation	Insulin Powder Formulation	Target Insulin Load	PLG Polymer	Surfactant	Measured Insulin Load
D	Formulation I	10% (w/w)	MEDISORB® 5050 DL PLG 2A	none	11.3%
E	Formulation I	10% (w/w)	MEDISORB® 5050 DL PLG 2.5A	none	11.5%
F	Formulation I	10% (w/w)	PLG-*co*-EMPO (MW=17kD)	none	11.9%
G	Formulation II	5% (w/w)	MEDISORB® 5050 DL PLG 2.5A	PLURONIC® F68	5.3%

The mixtures were sonicated and films were cast in polytetrafluoroethylene molds. The cast films were dried either at room temperature or at elevated temperatures under vacuum. Post-drying, the films were milled using a 24-tooth Retsch Ultra Centrifugal Mill (Retsch, Inc., Newtown, PA). The dried, milled particles were then compacted at machine settings of about 3000 to about 5000 pounds using a Carver Model C Press (Carver, Inc., Wabash, IN) and a cylindrical 3/8 inch die for about 30 seconds to 1 minute. The compacted pellets were then milled to yield a final powdered product. The product microparticles had a size of about 200 microns.

In general, *in vitro* release was highly varied for the compacted and milled material and depended on the particle formulation, the protein powder formulation, and the release medium. The *in vitro* insulin release at 24 hours from the various microparticle formulations ranged from about 13% to about 100% of the insulin released.

Specifically, the particle formulations of Table III were prepared and tested for *in vitro* release, and the results are discussed below. 10 milligrams of microparticles were added to 1 milliliter of either 0.1 M sodium phosphate, pH 7 at

37°C or Hepes buffer, pH 7 at 37°C. UV detection at 280 nanometers was used to measure the cumulative insulin release over time. FIG. 4 shows *in vitro* release of insulin from microparticles produced from Formulations D, E, and F in 0.1 M sodium phosphate, pH 7 at 37°C versus time (in days) and also from microparticles produced from Formulation G in Hepes buffer, pH 7 at 37°C versus time (in days). Table IV shows insulin integrity for particle Formulations D, E, and F as measured by size exclusion HPLC and peak area both initially and following 14 days in 0.1 M sodium phosphate, pH 7 at 37°C. Table IV indicates good insulin integrity even after 14 days in sodium phosphate solution.

Table IV: Insulin Integrity of Microparticles in 0.1 M sodium phosphate, pH 7 at 37°C

Particle Formulation	**Insulin Integrity Initial Extraction (t=0)**	**Insulin Integrity Extraction after 14 days *in vitro***
D	97.9%	80.2%
E	96.7%	85.6%
F	100.0 %	91.2%

EXAMPLE 5

The following example describes the production of particles comprising the opiate antagonist naltrexone and poly(*d,l*-lactide-*co*-glycolide) polymer. The process involved the casting of a homogeneous film of naltrexone and polymer, drying the film, compacting the film, and then milling the compacted film to form an injectable composition. The powder particles were subsequently coated with a drug-free polymer shell to further control the release of naltrexone from the particles *in vivo* upon injection.

A drug/polymer solution was formed by co-dissolving naltrexone base (Mallinckrodt, Inc., St. Louis, MO) and poly(*d,l*-lactide-*co*-glycolide) polymer (MEDISORB® DL PLG polymer, Alkermes, Inc., Cincinnati, OH) in either acetone

or methylene chloride. The concentration of polymer in solvent was about 10 to 30% (w/w). The solution was transferred to a polytetrafluoroethylene mold and was dried overnight at room temperature. The semi-dry films were then frozen in liquid nitrogen and milled using a Fluid Air Granumill Jr. (Fluid Air, Inc., Aurora, IL) to increase surface area for further solvent removal. The milled semi-dry films were then dried under vacuum to remove remaining solvent. The resulting dry powder was collected and compacted using a Carver Lab Model C Press (Carver, Inc., Wabash, IN) and a 3/8 inch cylindrical die set. The dry powder was compacted at a machine setting of about 2000-3000 pounds for 30 seconds, thus forming densified pellets. The pellets were frozen in liquid nitrogen and milled to form a free flowing, injectable, drug-loaded powder. The size of the resulting particles was less than about 200 microns. The powder was transferred to a vessel for storage. Powders were produced having 30%, 40% and 50% naltrexone by weight and using various poly(*d,l*-lactide-*co*-glycolide) polymers.

Naltrexone-containing particles produced using the above process demonstrate that dense polymer/drug particles can be produced by a process wherein the process of forming a polymer/drug matrix is decoupled from the final product morphology.

EXAMPLE 6

This example describes a study of the *in vitro* release of naltrexone from polymer coated injectable particles produced as in Example 5 and having compositions as indicated in Tables V and VI. Polymers used included a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 3.5A polymer and MEDISORB® 5050 DL PLG 4A polymer, Alkermes, Inc., Cincinnati, OH); a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an methyl ester end group (MEDISORB® 5050 DL PLG 4M polymer, Alkermes, Inc., Cincinnati, OH); PLG-*co*-EMPO; and MEDISORB® 6535 High IV DL PLG polymer (Alkermes, Inc., Cincinnati, OH).

Naltrexone load of the prepared particles was determined using either nitrogen analysis or by ultraviolet (UV) analysis of a sodium hydroxide/microparticle solution. Naltrexone load is also shown in Tables V and VI.

Naltrexone load in the microparticles was also determined by nitrogen analysis using a CHN elemental analyzer. Approximately 1 to 5 milligram samples of microparticles were combusted at 980°C in an oxygen atmosphere to produce nitrogen and nitrogen oxides. The gas stream was reduced over copper metal at 700°C to produce elemental nitrogen that was quantified by a thermal conductivity detector. NIST traceable acetanilide was used as the assay standard.

Naltrexone load in the microparticles was determined by dissolving approximately 10 milligrams of naltrexone loaded microparticles in 10 milliliters of 1 N sodium hydroxide for 2-4 hours. After the sample was fully dissolved, the naltrexone content was determined by UV analysis at 292 nanometers.

Twenty four hour *in vitro* release of naltrexone from the microparticles was determined by hydrating approximately 5 milligrams of naltrexone loaded microparticles in 3 milliliters of 150 mM sodium phosphate buffer at pH 7.0. The hydrated samples were mixed by hand shaking to fully wet the microparticles and then were placed into a 37°C incubator for twenty four hours. At the end of the incubation period, the supernatant was removed from the system and the naltrexone content was determined by UV analysis or Reverse Phase High Performance Liquid Chromatography (RP-HPLC) using a Hewlett Packard 1090 HPLC system equipped with a 100 x 4.6 mm YMC phenyl column (YMC Cat# PH12S03-1046WT; YMC, Inc., Milford, MA).

Table V: Naltrexone *in vitro* release from microparticles made using methylene chloride

Naltrexone Target Load	Polymer	Naltrexone Load (NaOH method)	24 hour *in vitro* Release (average, n=2)
30% (w/w)	PLG-*co*-EMPO	30%	90%
50% (w/w)	MEDISORB® 5050 DL PLG 3.5A	43%	87%
40% (w/w)	MEDISORB® 5050 DL PLG 3.5A	38%	66%
30% (w/w)	MEDISORB® 5050 DL PLG 3.5A	34%	57%
50% (w/w)	MEDISORB® 5050 DL PLG 4A	42%	102%
40% (w/w)	MEDISORB® 5050 DL PLG 4A	29%	89%
30% (w/w)	MEDISORB® 5050 DL PLG 4A	27%	79%
30% (w/w)	MEDISORB® 5050 DL PLG 4M	29%	84%

Table VI: Naltrexone *in vitro* release from microparticles made using acetone

Naltrexone Target Load	Polymer	Naltrexone Load (NaOH method)	24 hour *in vitro* Release (average, n=2)
50% (w/w)	MEDISORB® 5050 DL PLG 3.5A	51%	78%
40% (w/w)	MEDISORB® 5050 DL PLG 3.5A	39%	103%
30% (w/w)	MEDISORB® 5050 DL PLG 3.5A	24%	81%
50% (w/w)	MEDISORB® 5050 DL PLG 4A	45%	108%
40% (w/w)	MEDISORB® 5050 DL PLG 4A	42%	93%
30% (w/w)	MEDISORB® 5050 DL PLG 4A	31%	97%
30% (w/w)	MEDISORB® 6535 High IV DL PLG	29%	73%

Polymer coated particles, shown in Table VII, were prepared as described in Example 5 using a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 3.5A polymer, Alkermes, Inc., Cincinnati, OH), naltrexone, and methylene chloride as the solvent. The resulting powder contained a target drug load of up to 50% by weight. The milled powder particles were polymer coated using a Fluid Air Model 002 Dry/Granulator/Coater equipped with a 0.5L bowl (Fluid Air, Inc., Aurora, IL). The particles were fluidized in a bed of nitrogen gas and a coating solution of polymer in acetone was applied using an air/air atomizer.

The batch was split and coated with varying amounts of either a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 2A polymer, Alkermes, Inc., Cincinnati, OH) or a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an methyl ester end group (MEDISORB® 5050 DL PLG 2M polymer, Alkermes, Inc., Cincinnati, OH) as shown in Table VII.

Table VII: Naltrexone *in vitro* release from polymer coated microparticles

Target Naltrexone Load	**Coating Polymer**	**Naltrexone Load (N_2 method)**	**24 hour *in vitro* Release (average, n=2)**
50% (w/w)	none	39%	107%
45% (w/w)	MEDISORB® 5050 DL PLG 2A polymer	31%	79%
42.5% (w/w)	MEDISORB® 5050 DL PLG 2A polymer	30%	60%
40% (w/w)	MEDISORB® 5050 DL PLG 2A polymer	30%	53%
45% (w/w)	MEDISORB® 5050 DL PLG 2M polymer	33%	87%
42.5% (w/w)	MEDISORB® 5050 DL PLG 2M polymer	32%	74%
40% (w/w)	MEDISORB® 5050 DL PLG 2M polymer	32%	48%

EXAMPLE 7

This example describes a study of the *in vivo* release of naltrexone from polymer coated injectable particles produced as in Example 5.

To evaluate the release of drug from polymer coated particles, a 100 gram batch of powder was produced as described in Example 5 using a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 3.5A polymer, Alkermes, Inc., Cincinnati, OH), naltrexone, and methylene chloride as the solvent. The resulting powder contained a target drug load of up to 50% by weight. The milled powder particles were polymer coated using a Fluid Air Model 002 Dry/Granulator/Coater equipped with a 0.5L bowl (Fluid Air, Inc., Aurora, IL). The particles were fluidized in a bed of nitrogen gas and a coating solution of polymer in acetone was applied using an air/air atomizer.

The batch was split and coated with varying amounts of either a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 2A polymer, Alkermes, Inc., Cincinnati, OH) or a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an methyl ester end group (MEDISORB® 5050 DL PLG 2M polymer, Alkermes, Inc., Cincinnati, OH) as shown in Table VIII.

Table VIII: Coated Particle Formulations

Particle Formulation	Target Naltrexone Load	Coating Polymer	Coating Polymer Concentration (% by weight)
H	50	none	none
I	45	MEDISORB® 5050 DL PLG 2A polymer	10
J	42.5	MEDISORB® 5050 DL PLG 2A polymer	15
K	40	MEDISORB® 5050 DL PLG 2A polymer	20
L	45	MEDISORB® 5050 DL PLG 2M polymer	10
M	45.2	MEDISORB® 5050 DL PLG 2M polymer	15
N	40	MEDISORB® 5050 DL PLG 2M polymer	20

Particles produced according to the process described above and containing approximately 15-20 milligrams of naltrexone were suspended in an aqueous injection vehicle containing 3% carboxymethylcellulose (low viscosity), 0.1% polysorbate 20, and 0.9% sodium chloride. The suspension was injected subcutaneously into the mid-scapular region of male Sprague-Dawley rats (450 ± 50 g body weight, immunosuppressed).

Blood samples were collected via a lateral tail vein bleed after anesthesia with halothane. The blood was transferred to serum separator tubes and allowed to clot for 30 minutes at room temperature, centrifuged at >6000g for 5 minutes at 2-8°C, then stored at -70°C. Blood samples were collected at 2, 8, and 24 hours and then at 2, 4, 7, 10, 14, 21, 24, 28, 31, and 35 days after injection. Serum naltrexone concentration were determined by mass spectrometry.

FIG. 5 shows the *in vivo* release profile of naltrexone from variously coated particles over a 10 day study period. The *in vivo* results demonstrate that the release profile of naltrexone can be further controlled by applying a polymer coating to the relatively dense drug/polymer particles. The *in vivo* results also indicate that the initial burst of naltrexone release was reduced and also that the overall naltrexone release profile was improved.

EXAMPLE 8

This example describes the production of microparticles comprising bovine serum albumin (herein "BSA,"obtained from EM Science, Gibbstown, NJ) and an *in vivo* study preformed to test release of BSA from the microparticles.

A zinc/BSA complex was formed at a 10/1 molar ratio using spray freeze drying as earlier described. 74.7 grams of powdered zinc/BSA complex was suspended in 2371 milliliters of methylene chloride with 474 grams of a poly(*d,l*-lactide-*co*-glycolide) polymer having 50 mol% *d,l*-lactide, 50 mol% glycolide, and an acid end group (MEDISORB® 5050 DL PLG 2A polymer) and 4.7 grams $ZnCO_3$. This suspension was combined with a nitrogen gas stream and sprayed at 30 psi using a Spray Systems, Inc. Model #205070 Spray Nozzle (Wheaton, IL) into liquid nitrogen to form particles. The particles were recovered form the liquid nitrogen and the methylene chloride was extracted from the particles using excess ethanol. The resulting polymer/drug microparticles (15% zinc/BSA complex and 1% $ZnCO_3$ target load) were dried under vacuum for five days.

A portion of the polymer/drug microparticles thus formed were then compacted using a Carver Model C Press (Carver, Inc., Wabash, IN) at a machine setting of 4000 pounds to form wafers having a diameter of 3/8 inch and a thickness of about 1/8 of an inch. A portion of the wafers were fragmented by freezing the wafers in liquid nitrogen and then fracturing the frozen wafers using a razor blade thus forming implantable microparticles. The implantable microparticles had a size range of from about 200 to about 500 microns.

The compositions (polymer/drug microparticles, wafers and implantable microparticles) thus formed were administered to laboratory rats. Male Sprague-

Dawley rats (400 ± 50 grams) were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The animals were immunosuppressed using cyclosporine (SANDIMMUNE®, Novartis Pharmaceuticals Corp., East Hanover, NJ). Animals were divided into three test groups (n=3/group).

Animals in Group A were injected subcutaneously with the polymer/drug microparticles into the interscapular region. Each animal received a dose comprising approximately 50 milligrams of particles containing 7.5 milligrams BSA in a vehicle volume of 0.75 milliliters. The injection vehicle was 3% carboxymethylcellulose ('CMC') (low viscosity) and 0.1% TWEEN® 20 (*i.e.*, polyoxyethylene 20 sorbitan monooleate, TWEEN® is a trademark of ICI Americas, Inc.) in 0.9% aqueous sodium chloride.

The animals in Group B were implanted subcutaneously with 50 milligrams compressed wafers (total amount of BSA administered was 7.5 mg) into the interscapular region.

The animals in Group C were implanted subcutaneously with 50 milligrams implantable microparticles (total amount of BSA administered was 7.5 mg) into the interscapular region.

Blood samples were collected via a lateral tail vein after anesthesia with halothane. Blood samples were collected at predose, at 2, 4, 6, 10, and 24 hours and then at 2, 4, 7, 10, 14, 17, 21, 24, and 28 days after administration. The blood was transferred to serum separator tubes and allowed to clot for 30 minutes at room temperature, centrifuged at 6000g for 5 minutes at room temperature, and the serum stored at less than -70°C. Serum samples were analyzed using a BSA Enzyme-Linked Immuno-Sorbent Assay (ELISA) kit (Catalog #F030) provided by Cygnus Technologies (Wrentham, MA).

FIG. 6 shows BSA concentration in blood serum, in nanograms/milliliter, versus time, in days. The data demonstrate that the implantable microparticles gave a release profile with a C_{MAX} (*i.e.*, maximum BSA concentration in blood serum) lower than that of the uncompressed, unfragmented polymer/drug particles but higher than the implanted wafer. The implantable microparticles also showed higher

sustained concentrations of BSA, and a longer duration of release than that provided by the uncompressed, unfragmented polymer/drug particles.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

We claim:

1. A method for preparing an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:
   (a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;
   (b) removing the solvent from the mixture, thereby forming a polymer/ biologically active agent matrix;
   (c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and
   (d) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

2. The method of Claim 1 wherein the biologically active agent is dissolved in the mixture.

3. The method of Claim 1 wherein the biologically active agent is suspended in the mixture.

4. The method of Claim 1 further comprising the step of fragmenting the matrix prior to compressing the matrix.

5. The method of Claim 1 wherein the biocompatible polymer is biodegradable.

6. The method of Claim 1 wherein the biocompatible polymer is 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, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetals, polycyanoacrylates, polyetheresters,

polycaprolactone, poly(dioxanone)s, poly(alkylene alkylate)s, polyurethanes, and blends and copolymers thereof.

7. The method of Claim 6, wherein the polymer is poly(lactide-*co*-glycolide)-*co*-EMPO.

8. The method of Claim 1 wherein the solvent is removed by evaporation.

9. The method of Claim 1 wherein the solvent is removed by sublimation.

10. The method of Claim 1 wherein the mixture is cast as a film prior to removal of the solvent.

11. The method of Claim 1 wherein the matrix is compressed using a press and die apparatus.

12. The method of Claim 1 wherein the compressed matrix is fragmented by milling.

13. The method of Claim 12 wherein the milling is selected from the group consisting of jet milling, centrifugal milling and hammer milling.

14. The method of Claim 1 wherein the compressed matrix is fragmented under cryogenic conditions.

15. The method of Claim 1 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 1 to about 1000 microns.

16. The method of Claim 1 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 500 microns or less.

17. A method for forming an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:

(a) forming a mixture of a biologically active agent, a biocompatible polymer and a polymer solvent;

(b) forming droplets of the mixture;

(c) freezing the droplets, thereby forming frozen droplets;

(d) extracting the polymer solvent from the frozen droplets into a non-solvent, thereby forming a polymer/biologically active agent matrix;

(e) compressing the matrix, thereby forming a compressed matrix; and

(f) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

18. The method of Claim 17 wherein the biocompatible polymer is biodegradable.

19. The method of Claim 17 wherein the biocompatible polymer is 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, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyaetals, polycyanoacrylates, polyetheresters, polycaprolactone, poly(dioxanone)s, poly(alkylene alkylate)s, polyurethanes, and blends and copolymers thereof.

20. The method of Claim 17 wherein the droplets are frozen using a liquefied gas.

21. The method of Claim 17 wherein the droplets are formed by atomizing the mixture.

22. The method of Claim 17 wherein the droplets are microdroplets.

23. The method of Claim 17 wherein the matrix is compressed using confined pressure compaction.

24. The method of Claim 17 wherein the matrix is compressed using a press and die apparatus.

25. The method of Claim 17 wherein the matrix is compressed in the presence of a coolant.

26. The method of Claim17 wherein the compressed matrix is fragmented by milling.

27. The method of Claim 26 wherein the compressed matrix is fragmented by milling selected from the group consisting of jet, centrifugal and hammer milling.

28. The method of Claim 17 wherein the compressed matrix is fragmented in the presence of a coolant.

29. The method of Claim 17 wherein the compressed matrix is fragmented under cryogenic conditions.

30. The method of Claim 17 wherein the compressed matrix is fragmented matrix is fragmented to produce microparticles having a volume median particle size of about 1 micron to about 1000 microns.

31. The method of Claim 17 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 500 microns or less.

32. The method of Claim 17 wherein the biologically active agent is suspended in the mixture.

33. The method of Claim 17 wherein the biologically active agent is dissolved in the mixture.

34. A method for treating a patient in need of therapy comprising:

administering to the patient a therapeutically effective amount of the injectable microparticle composition made by the method of Claim 17.

35. A method for treating a patient in need of a sustained release of a biologically active agent, comprising:

administering to the patient a therapeutically effective amount of an injectable microparticle composition for sustained release of a biologically active agent prepared by a process including the steps of:

(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;

(b) removing the solvent from the mixture, thereby forming a polymer/ biologically active agent matrix;

(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and

(d) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

36. The method of Claim 35 wherein the biologically active agent is dissolved in the mixture.

37. The method of Claim 35 wherein the biologically active agent is suspended in the mixture.

38. The method of Claim 35 wherein the process for preparing the injectable microparticle composition further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

39. The method of Claim 35 wherein the biologically active agent is an antipsychotic drug.

40. The method of Claim 39 wherein the biologically active agent is selected from the group consisting of aripiprazole, olanzapine and risperidone.

41. The method of Claim 39 wherein the patient suffers from an affective disorder.

42. The method of Claim 41 wherein the patient suffers from a condition selected from the group consisting of schizophrenia, depression, and anxiety.

43. Microparticles produced by a process comprising the steps of:

(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;

(b) removing the solvent from the mixture, thereby forming a polymer/biologically active agent matrix;

(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and

(d) fragmenting the compressed matrix, thereby forming the microparticles.

44. The method of Claim 43 wherein the biologically active agent is dissolved in the mixture.

45. The method of Claim 43 wherein the biologically active agent is suspended in the mixture

46. The microparticles of Claim 43 wherein the process for preparing the microparticles further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

47. The microparticles of Claim 43 wherein the microparticles have a volume median particle size of about 1 micron to about 1000 microns.

48. The microparticles of Claim 43 wherein the microparticles have a volume median particle size of about 500 microns or less.

49. A pharmaceutical composition comprising the microparticles of Claim 43.

50. Microparticles produced by a process comprising the steps of:
(a) forming a mixture of a biologically active agent, a biocompatible polymer and a polymer solvent;
(b) forming droplets of the mixture;
(c) freezing the droplets, thereby forming frozen droplets;
(d) extracting the polymer solvent from the frozen droplets into a non-solvent, thereby forming a polymer/biologically active agent matrix;
(e) compressing the matrix, thereby forming a compressed matrix; and
(f) fragmenting the compressed matrix, thereby forming the microparticles.

51. The microparticles of Claim 50 wherein the process for preparing the microparticles further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

52. The microparticles of Claim 50 wherein the microparticles have a volume median particle size of about 1 micron to about 1000 microns.

53. The microparticles of Claim 50 wherein the microparticles have a volume median particle size of about 500 microns or less.

54. A pharmaceutical composition comprising the microparticles of Claim 50 and a physiologically acceptable vehicle.

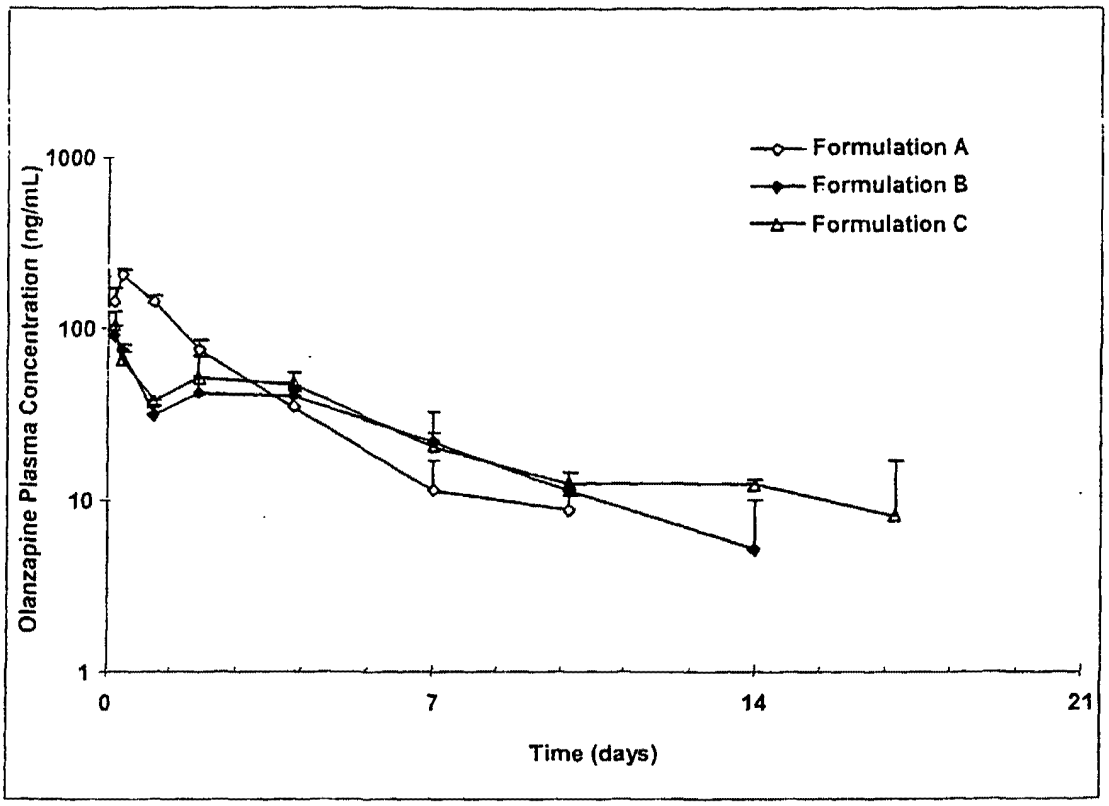

Formulation A
Formulation B
Formulation C
Olanzapine Plasma Concentration (ng/mL)
1000
100
10
1
0
7
14
21
Time (days)

FIG. 1

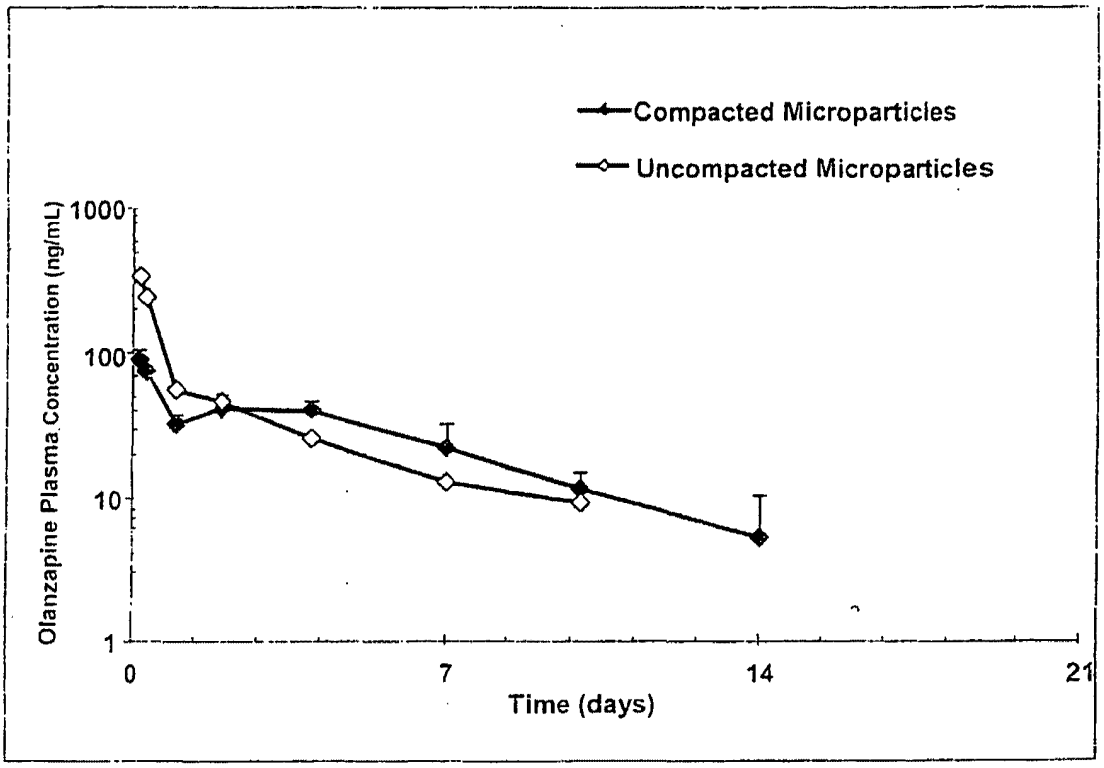

Compacted Microparticles
Uncompacted Microparticles
Olanzapine Plasma Concentration (ng/mL)
1000
100
10
1
0
7
14
21
Time (days)

FIG. 2

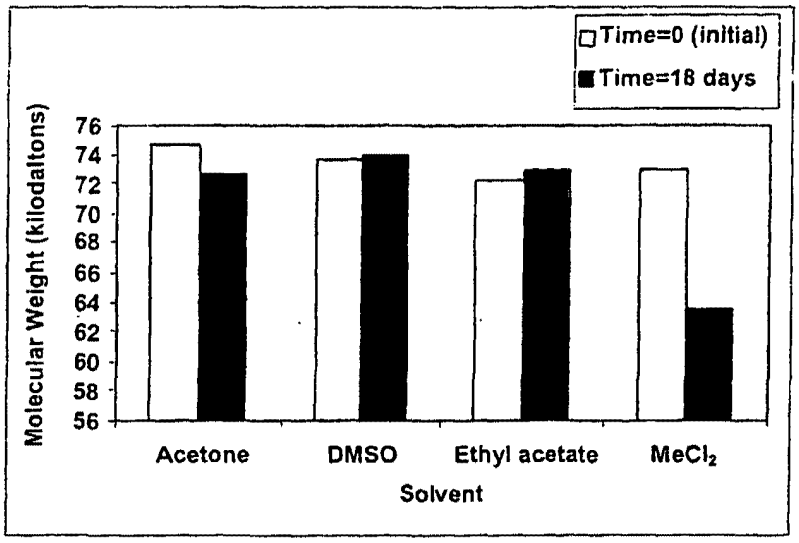

Time=0 (initial)
Time=18 days
Molecular Weight (kilodaltons)
76
74
72
70
68
66
64
62
60
58
56
Acetone
DMSO
Ethyl acetate
MeCl2
Solvent

FIG. 3

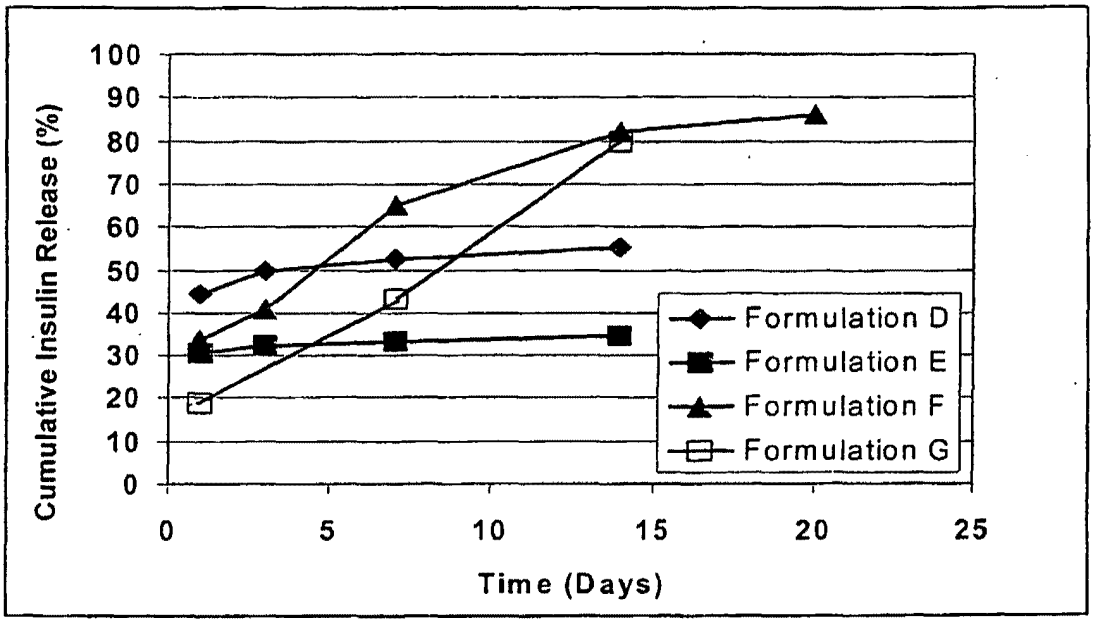

Cumulative Insulin Release (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (Days)
Formulation D
Formulation E
Formulation F
Formulation G

FIG. 4

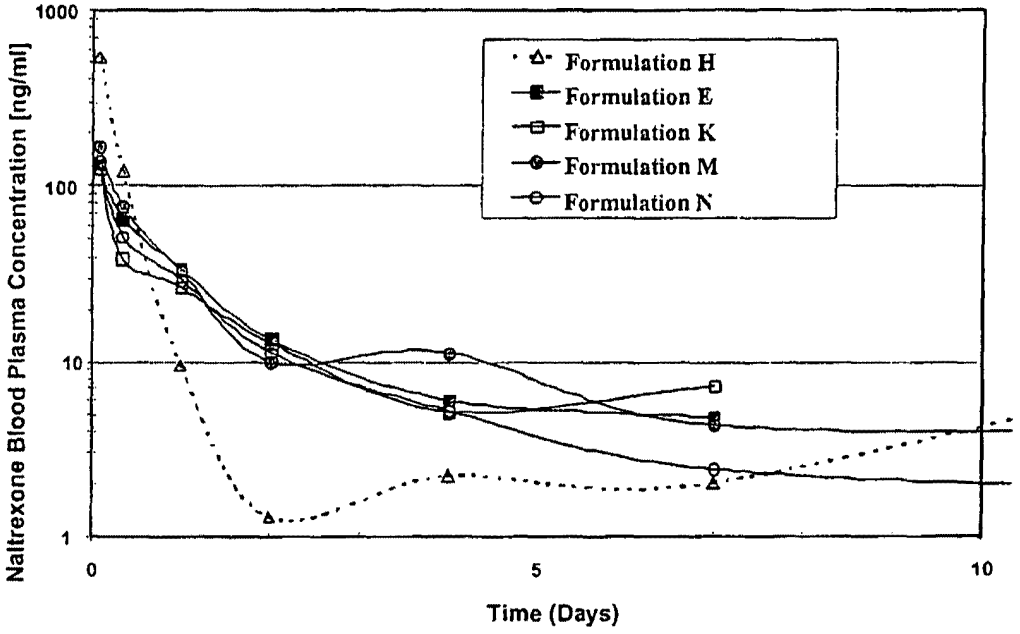

1000
100
10
1
0
5
10
Naltrexone Blood Plasma Concentration [ng/ml]
Time (Days)
Formulation H
Formulation E
Formulation K
Formulation M
Formulation N

FIG. 5

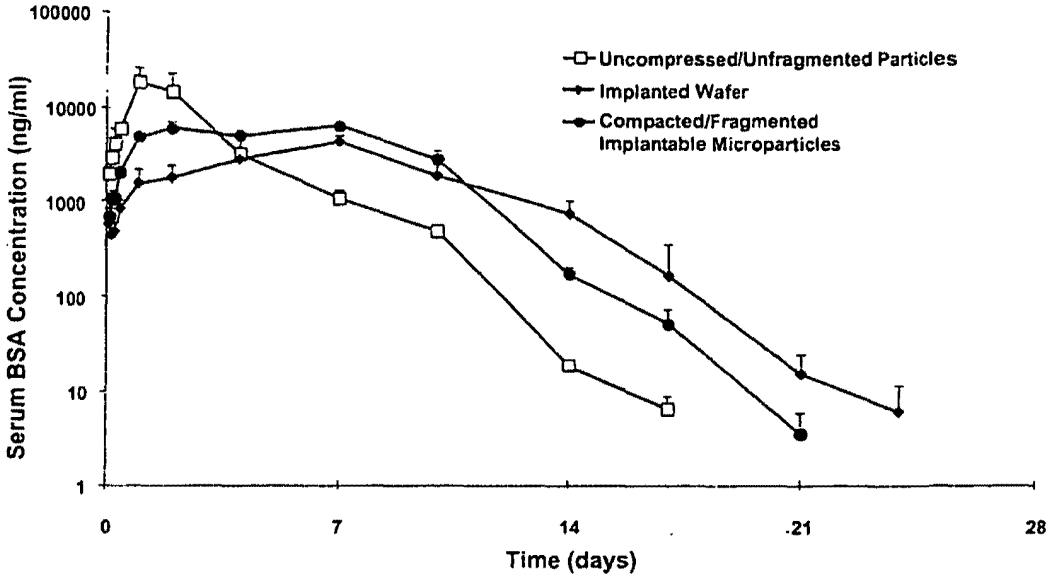

100000
10000
1000
100
10
1
Serum BSA Concentration (ng/ml)
0
7
14
21
28
Time (days)
Uncompressed/Unfragmented Particles
Implanted Wafer
Compacted/Fragmented
Implantable Microparticles

FIG. 6

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
12 May 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF PREPARING SUSTAINED RELEASE MICROPARTICLES

(57) Abstract: The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent. The invention provides an improved process for the preparation of microparticles, wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/drug matrix. The method includes the steps of (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/drug matrix can be provided by any suitable method.

WO 2004/064752 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/001501

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92/19226 A (DYNAGEN INC) 12 November 1992 (1992-11-12) page 20, paragraph 2 - page 12, paragraph 2 examples ----- -/--	1,2,5,6, 8,10-12, 14-16, 35,36, 39, 41-44, 47-49

[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
4 August 2004	18 MAR 2005

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	Epskamp, S

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHARON A C ET AL: "Development of drug delivery systems for use in treatment of narcotic addiction." NIDA RESEARCH MONOGRAPH. 1981, vol. 28, 1981, pages 194-213, XP002291127 ISSN: 1046-9516 abstract page 196, paragraph 2 - page 197, paragraph 1 page 207, paragraph 2 - page 209, paragraph 2	1,2,5,6, 8,10-12, 14-16, 35,36, 39, 41-44, 47-49
X	WO 94/07469 A (DYNAGEN INC) 14 April 1994 (1994-04-14) page 3, last paragraph page 16, paragraph 2 - last paragraph examples 7,8 claims 25-35	1,3,5,6, 8,10-12, 14-16, 35,37, 39, 41-43, 45,47-49
X	US 5 192 741 A (DEGHENGHI ROMANO ET AL) 9 March 1993 (1993-03-09) column 1, line 6 - line 12 column 2, line 14 - line 35 examples claims	1,3,5,6, 8,10-12, 14-16, 35,37, 39, 41-43, 45,47-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/001501

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16, 35-49

Method for preparing an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:
(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;
(b) removing the solvent from the matrix, thereby forming a polymer/active agent matrix;
(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and
(d) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

---

2. claims: 17-34, 50-54

Method for forming an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:
(a) forming a mixture of a biologically active agent, a biocompatible polymer and a polymer solvent;
(b) forming droplets of the mixture;
(c) freezing the droplets, thereby forming frozen droplets;
(d) extracting the polymer solvent from the frozen droplets into a non-solvent, thereby forming a polymer/active agent matrix;
(e) compressing the matrix, thereby forming a compressed matrix; and
(f) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9219226 A	12-11-1992	AU 657973 B2	30-03-1995
		AU 2016092 A	21-12-1992
		AU 2154892 A	21-12-1992
		CA 2102507 A1	08-11-1992
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WO 9407469 A	14-04-1994	AU 4932493 A	26-04-1994
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		SE 503406 C2	10-06-1996
		SE 8803321 A	22-03-1989
		US 5776885 A	07-07-1998
		ZA 8806827 A	30-05-1989

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Elmore, Craig & Vanstone
Strategic Intellectual Property

FACSIMILE COVER SHEET

Date: July 15, 2005

To: Notice to File Missing Parts of NonProvisional Application

From: Carolyn S. Elmore
Registration No. 37,567

Fax Number: (703) 746-4060

Subject: **Paper:** Reply to Notice to File Missing Parts of Non-Provisional Application
Docket No.: 4000.3010 US1
Applicants: Elliot Ehrich
Serial No.: 11/083,167
Filing Date: March 17, 2005

Number of pages including this cover sheet 11

Please confirm receipt of facsimile: Yes X No _____

Comments:

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Elmore, Craig & Vanstone, P.C., 209 Main Street, Chelmsford, MA 01863, USA. voice: (978) 251-3509 / fax: (978) 251-3973 . www.elmorecraig.com

PAGE 1/11 * RCVD AT 7/15/2005 1:32:33 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7464060 * CSID: * DURATION (mm-ss):04-00

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Docket No. 4000.3010 US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elliot Ehrich

Application No.: 11/083,167 Group: 1614

Filed: March 17, 2005 Examiner: Not Assigned

Confirmation No.: 8002

For: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

CERTIFICATE OF MAILING OR TRANSMISSION
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:
Hollie Wakefield 7-15-05
Signature Date
HOLLIE WAKEFIELD
Typed or printed name of person signing certificate

REPLY TO NOTICE TO FILE MISSING PARTS OF APPLICATION

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

Sir:

In reply to the Notice to File Missing Parts dated April 15, 2005, the following documents and fees are being submitted for filing in the captioned application.

[X] **EXECUTED DECLARATION FOR PATENT APPLICATION**
(Separate transmittal letter and postcard not required)

[X] **POWER OF ATTORNEY DOCUMENT**
[ ] **GRANTED BY INVENTOR(S)**
[X] **GRANTED BY ASSIGNEE, INCLUDING Statement under 37 C.F.R. 3.73(b)**
(Separate transmittal letter and postcard not required)

[ ] **PRELIMINARY AMENDMENT**
(Separate transmittal letter and postcard not required)

[ ] **FILING FEE** – WITH Fee Transmittal for Patent Applications in duplicate
Fee calculations based on:
[ ] Claims as originally filed
[ ] Claims upon entry of the Preliminary Amendment filed herewith
(Separate transmittal letter and postcard not required)

PAGE 2/11 * RCVD AT 7/15/2005 1:32:33 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7464060 * CSID: * DURATION (mm-ss):04-00

Application No. 11/083,167

[X] **SURCHARGE** – SURCHARGE FEE OF $130
(Separate transmittal letter and postcard not required)

[ ] **SEQUENCE LISTING** - Filed concurrently and is attached
(Separate transmittal letter and postcard required)

[ ] **REPLACEMENT DRAWINGS**
[ ] Sheets of replacement drawings consisting of Figs. 1 – [ ] are enclosed.
(Separate transmittal letter and postcard not required)

[X] **PETITION FOR EXTENSION OF TIME**
[X] Applicants hereby petition to extend the time to respond to the Notice to File Missing Parts dated April 15, 2005 for one month from June 15, 2005 to July 15, 2005. Please charge the appropriate fee $120.00 to Deposit Account No. 502807 to cover the fees required.
[ ] A [ ] month extension of time to respond to the Notice to File Missing Parts dated [ ] was filed on [ ] with payment of a $[ ] fee.
[ ] Applicant hereby petitions for an additional [ ] month extension of time to respond to the Notice to File Missing Parts. The appropriate fee of $[ ] is included in the enclosed check.
(Separate Petition for Extension of Time and postcard not required)

[ ] **REQUEST FOR CORRECTED FILING RECEIPT** – Filed concurrently and is attached.
(Separate transmittal letter and postcard required)

[ ] **STATEMENT CLAIMING SMALL ENTITY STATUS**
[ ] Applicant claims small entity status.
[ ] Is enclosed herewith *(Separate transmittal letter and postcard not required)*
[ ] In view of the small entity status of the captioned application, we hereby request a reimbursement of 50% of the filing fees in the amount of $[ ] which were paid on [ ] to be deposited in Deposit Account No.

Please charge $250.00 to Deposit Account No. 502807 to cover the fees required for filing the indicated documents. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 502807.

Respectfully submitted,

ELMORE, CRAIG & VANSTONE, P.C.

By
Carolyn S. Elmore
Registration No.: 37,567
Tel.: (978) 251-3509
Fax: (978) 251-3973

N. Chelmsford, Massachusetts 01863
Date: **July 15, 2005**

PAGE 3/11 * RCVD AT 7/15/2005 1:32:33 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/0 * DNIS:7464060 * CSID: * DURATION (mm-ss):04-00

DOCKET NO. 4000.3010 US1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Elliot Ehrich

Application No.: 11/083,167 Group: 1614

Filed: March 17, 2005 Examiner: Not Assigned

Confirmation No.: 8002

For: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

CERTIFICATE OF MAILING OR TRANSMISSION
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

7-15-05 Hollie Wakefield
Date Signature

HOLLIE WAKEFIELD
Typed or printed name of person signing certificate

Mail Stop Notice to File Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

07/18/2005 TLO111 00000025 502807 11083167
01 FC:1251 120.00 DA

Sir:

Transmitted herewith is the Notice to File Missing Parts for filing in the above-identified application.

[ ] Small entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a Small Entity Statement previously submitted.

[ ] A Small Entity Statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.

The fee has been calculated as shown below:

	(COL. 1)			(COL. 2)	(COL. 3)		SMALL ENTITY			OTHER THAN SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE	ADDIT. FEE	OR	RATE	ADDIT. FEE
TOTAL	25	MINUS	*	25	0		X $25	$		X $50	$0
INDEP	7	MINUS	**	7	0		X $100	$		X $200	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM							+ $180	$		+ $360	$
* not fewer than 20 ** not fewer than 3							TOTAL =	$ 0		TOTAL =	$

11/083,167

Please charge Deposit Account No. 502807 for the following fees:				
	[X]	Petition for one month Extension of Time	$	120
	[ ]	Amendment Fee	$	
	[X]	Other Fees: Late oath or declaration Surcharge		130
			$	
			$	
		TOTAL:	$	250
A check is enclosed in payment of the following fees:				
	[ ]	Petition for [ ] month Extension of Time	$	
	[ ]	Amendment Fee	$	
	[ ]	Other Fees:		
			$	
			$	
		TOTAL:	$	0

[X] 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.

Respectfully submitted,

ELMORE, CRAIG & VANSTONE, P.C.

By _____
Carolyn S. Elmore
Registration No.: 37,567
Telephone (978) 251-3509
Facsimile (978) 251-3973

N. Chelmsford, Massachusetts 01863
Dated: **July 15, 2005**

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 NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1

CONFIRMATION NO. 8002

00038421
ELMORE CRAIG, P.C.
209 MAIN STREET
N. CHELMSFORD, MA 01863

FORMALITIES LETTER

OC000000015761013

Date Mailed: 04/15/2005

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(f) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$130** for a Large Entity

- **$130** Late oath or declaration Surcharge.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

07/18/2005 TL0111 00000025 502807 11083167
02 FC:1051 130.00 DA

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

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JUL 15 2005

DOCKET NO: 4000.3010 US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Declaration for Patent Application

[ ] Supplemental (37 C.F.R. §1.67)

As a named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated next to my name;

I believe I am the original, first and sole inventor (if only one name is listed) or an original, first and joint inventor (if plural names are listed in the signatory page(s) commencing at page 2 hereof) of the subject matter which is claimed and for which a patent is sought on the invention entitled

NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on March 17, 2005 as United States Application

Number or PCT International Application No. 11/083,167

and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. ' 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

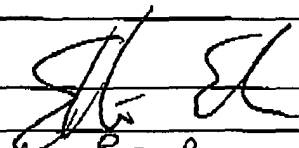
I hereby claim foreign priority benefits under 35 U.S.C. 119 or 365 of any foreign application(s) for patent or inventor's certificate, or of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Not Claimed	Certified Copy Filed? YES	NO
(Number)	(Country)	(Day/Month/Year filed)	[ ]	[ ]	[ ]
(Number)	(Country)	(Day/Month/Year filed)	[ ]	[ ]	[ ]
(Number)	(Country)	(Day/Month/Year filed)	[ ]	[ ]	[ ]

DOCKET NO: 4000.3010 US1

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

Full name of sole
Or first inventor Elliot Ehrich

Inventor's Signature  Date 6/14/05

Residence Two Oak Meadow Road
Lincoln, MA 01773

Citizenship US

Mailing Address Same as above

PTO/SB/81 (11-04)
Approved for use through 11/30/2005. OMB 0651-0035
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.

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	11/083,167
Filing Date	March 17, 2005
First Named Inventor	Elliot Ehrich
Title	"Naltrexone Long Acting..."
Art Unit	
Examiner Name	
Attorney Docket Number	4000.3010 US1

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 000038421

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

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OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Fax			

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)

SIGNATURE of Applicant or Assignee of Record

Signature	Claire M Vasios	Date	7/13/05
Name	Claire M Vasios, Ph.D.	Telephone	617-583-6165
Title and Company	V.P. of Intellectual Property		

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 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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/96 (09-04)
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Elliot Ehrich

Application No./Patent No.: 11/083,167 Filed/Issue Date: March 17, 2005

Entitled: NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

Alkermes Controlled Therapeutics II, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Claire M. Vasios — Signature — 7/13/05 — Date

Claire M. Vasios, Ph.D. — Printed or Typed Name — 617-583-6165 — Telephone Number

V.P. of Intellectual Property — Title

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/083,167	03/17/2005	Elliot Ehrich	4000.3010 US1

CONFIRMATION NO. 8002

00038421
ELMORE CRAIG, P.C.
209 MAIN STREET
N. CHELMSFORD, MA 01863

FORMALITIES LETTER

OC000000015761013

Date Mailed: 04/15/2005

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(f) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$130** for a Large Entity

- **$130** Late oath or declaration Surcharge.

Replies should be mailed to: Mail Stop Missing Parts
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A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (703) 308-1202

PART 3 - OFFICE COPY

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	4000.3010 US1
First Inventor	Elliot Ehrich
Title	"Naltrexone Long Acting..."
Express Mail Label No.	EV 540089543 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☑ **Fee Transmittal Form** (e.g., PTO/SB/17)
   (Submit an original and a duplicate for fee processing)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification** [*Total Pages* 34]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☑ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 4]
5. **Oath or Declaration** [*Total Sheets* _____]
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☐ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

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ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee _____
10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment**
14. ☑ **Return Receipt Postcard** (MPEP 503)
    (Should be specifically itemized)
15. ☐ **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ Other: _____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: .....

Prior application information: *Examiner* _____ *Art Unit:* _____

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 00038421 *OR* ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Fax	

Signature	Darlene Vanstone	Date	March 17, 2005
Name (Print/Type)	Darlene A. Vanstone	Registration No. (Attorney/Agent)	35,729

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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 2050

Complete if Known	
Application Number	
Filing Date	March 17, 2005
First Named Inventor	Elliot Ehrich
Examiner Name	
Art Unit	
Attorney Docket No.	4000.3010 US1

METHOD OF PAYMENT (check all that apply)

☑ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 502807 Deposit Account Name: Elmore Craig, P.C.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

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.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	1000
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)		Fee Paid ($)
25	- 20 or HP =	5	x 50	=	250

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
7	- 3 or HP =	4	x 200	=	800

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), 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).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)		Fee Paid ($)
38	- 100 =	0	/ 50 =	_____ (round up to a whole number)	x _____	=	0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): _____	

SUBMITTED BY

Signature	Darlene Vanstone	Registration No. (Attorney/Agent) 35,729	Telephone (978)251-3509
Name (Print/Type)	Darlene A. Vanstone		Date March 17, 2006

This collection of information is required by 37 CFR 1.136. 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 30 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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Date: 3/17/05 Express Mail Label No. EV 540089543 US

Inventor: Elliot Ehrich

Attorney's Docket No.: 4000.3010 US1

NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/564,542, filed on April 22, 2004. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Alcohol dependence is a chronic disorder that results from a variety of genetic, psychological and environmental factors. Traditional treatment has consisted of two phases: detoxification and rehabilitation. Detoxification ameliorates the symptoms and signs of withdrawal; rehabilitation helps the patient avoid future problems with alcohol. In the past, most rehabilitative treatments have been psychosocial. With advances in neurobiology, there is increasing interest in drug therapy for alcohol dependence. For a discussion of the development of this field, see Swift, R., Drug *Therapy for Alcohol Dependence*, NEJM, May 13, 1999, 1482-1490. Yet, the successful treatment of alcoholism has many serious challenges and complications. Patient compliance is a serious problem.

Accordingly, there is a need for improving naltrexone therapies.

SUMMARY OF THE INVENTION

The inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone. As such, 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 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 over the course of the month than that achieved by 50 mg/day oral administration.

The inventions also include a method of treating an individual in need of naltrexone comprising administering a long acting formulation in a dose comprising at least about 160 mg of naltrexone, preferably between about 160 mg and about 480 mg naltrexone, more preferably between about 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.

The inventions also include a method of treating an individual in need of naltrexone comprising administering naltrexone, such as in a long acting formulation, 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.

The invention also includes a method of treating an individual in need of naltrexone comprising administering naltrexone as a long acting formulation in the absence of concomitant psychosocial treatment/intervention.

The inventions include 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.

The inventions include a method of treating an individual in need of naltrexone comprising administering a 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 days, such as within ten days, before said administration.

BRIEF SUMMARY OF THE DRAWINGS

Figures 1A-1C shows the cumulative mean event rate of heavy drinking during the study by treatment group and gender. As an example, at day 100, the mean number of cumulative heavy drinking days for the overall study population was 22.3 for the

long-acting naltrexone 380 mg patients, 27.3 for long-acting naltrexone 190 mg patients, and 30.0 for placebo patients.

Figure 2 shows median heavy drinking days per month for each treatment group, overall and by gender. Asterisks represent interquartile range (25%, 75%).

DETAILED DESCRIPTION OF THE INVENTION

The inventions relate to the administration of a naltrexone containing formulation, preferably a long acting naltrexone formulation, to patients in need thereof and to the use of naltrexone in the manufacture of medicaments for use in such methods.

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 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. 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®.

The inventions also include a method of treating an individual in need of naltrexone comprising administering naltrexone, such as in a long acting formulation, 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. In this embodiment, it was unexpectedly discovered that good to excellent results could be achieved without either requiring alcohol abstinence or requiring alcohol consumption during therapy, as taught by Sinclair, United States Patent No. 4,882,335. Further, good to excellent results were achieved in patients that did not receive oral naltrexone in advance of the long acting formulation administration, contrary to the clinical protocols

as taught by Drug Abuse Sciences. Thus, the inventions also include administering a long acting formulation to individuals who did not receive a prior oral dose of naltrexone, for example, within 3, such as within about 5 days or about 10 days of commencing therapy.

As such, the inventions also include a method of treating an individual in need of naltrexone comprising administering a long acting formulation in a dose comprising between about 160 mg and 240 mg of naltrexone or about 310 mg to about 480 mg of naltrexone and formulations for use in the methods described herein. Preferred formulations are administered in a dose comprising about 190 mg or about 380 mg naltrexone.

The naltrexone can be in any form, including anhydrous, hydrate, solvate or salt forms or combinations thereof. It can be crystalline or non-crystalline or combinations thereof. A preferred naltrexone form comprises a naltrexone ethanolate, such as that described in United States Patent Application No. 60/475,863, filed on June 4, 2003, which is incorporated herein by reference and/or anhydrous naltrexone. A particularly preferred naltrexone form is that produced by the encapsulation process described in United States Patent No. 6,264,987, by Wright et al., which is incorporated herein by reference.

The naltrexone can be combined with any of the well-known biodegradable and bioerodible carriers, such as polylactides, poly(lactic acids) and poly-lactide-co-glycolides and collagen formulations. A particularly preferred polymer is a polylactide-co-glycolide polymer which possesses a molecular weight of at least 100,000 daltons, such as those described below in the exemplification. Such materials may be in the form of solid implants, sponges, and the like.

As stated above, the naltrexone is preferably in a long acting formulation. Long acting (also referred to as extended, sustained, or controlled release) preparations may be achieved through the use of polymers (preferably poly-lactide or poly-lactide-co-glycolide polymers) to entrap or encapsulate the naltrexone described herein. Extended release formulations can be made by spray drying polymer-drug mixtures, emulsion-based technologies, coacervation based technologies, film casting, extrusion based

technologies and other processes to manufacture polymer-drug microparticles possessing an extended release profile. Examples of suitable extended release technologies that can be used to incorporate the novel naltrexone forms described herein include, without limitation, the MEDISORB® technology, as described in, for example, US Patent Nos. 6,264,987 to Wright, 5,654,008 and/or 5,792,477, for example; the PROLEASE® technology, as described, for example in US Patent 6,358,443 to Herbert; the technologies described by Southern Research Institute, as described for example in US Patents 6,306,425 and 5,407,609; and "Method of Preparing Sustained Release Microparticles," U.S. Application No. 60/441,946, filed January 23, 2003, and the technologies described by Alza Corp., including the ALZAMER® Depot injection technology. The contents of these patents are incorporated herein by reference in their entirety.

In another embodiment, the novel naltrexone forms described herein may be used in combination with other treatments including but not limited to psychotherapy and/or other medications. Other medications that may be combined with the long acting naltrexone of the invention include but are not limited to anticonvulsants (see U.S. Patent Application Number 60/554,658 and copending application Attorney Docket Number 4000.3007 US1 filed on March 17, 2005, incorporated herein by reference), dopamine D2 partial agonists (see U.S. Patent Application Number 60/554,785 and copending application Attorney Docket Number 4000.3008 US2 filed on march 17, 2005, incorporated herein by reference) and cannabinoid receptor antagonist. Examples of anticonvulsants useful in conjunction with the present invention include but are not limited to carbamezepine, valproic acid, lamotrigine, gabapentin, topiramate, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, ethosuximide, methsuximinde, phensuximide, trimethadione, phenacemide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, clobazam, sulthiame, dilantin, zolpidem tartrate, zaleplon, indiplon, and zopiclone. Examples of dopamine D2 partial agonists useful in the present invention include but are not limited to Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3- ,4-dihydro

carbostyril or 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro -2(1H)-quinolinone, and the partial dopamine agonist (-)3-(3-hydroxyphenyl)-N-n-propylpiperidine [(-)-3PPP, see U.S. Pat. No. 4,719,219].

In a preferred embodiment, the long acting formulation delivers therapeutically beneficial amounts of naltrexone to the patient for a period of at least one week, preferably at least about two weeks, more preferably at least about 3 or about 4 or more weeks. A four week delivery is often referred to as a monthly delivery.

In one preferred embodiment, the naltrexone is present in the extended release device or formulation in an amount of at least about 5% by weight, preferably at least about 10% by weight, more preferably at least about 30% by weight, such as about 35% by weight naltrexone of the total weight of the device, or formulation.

Alternatively, instead of incorporating naltrexone into polymeric particles, it is possible to entrap these materials in microparticles prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatine-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin, microparticles, microemulsions, nanoparticles, and nanocapsules), or in macroemulsions.

When the composition is to be used as an injectable material, including but not limited to needle-less injection, it can be formulated into a conventional injectable carrier. Suitable carriers include biocompatible and pharmaceutically acceptable solutions. The injection can be intramuscular or subcutaneous.

While the formulation may contain additional excipients, as is well known in the art, the present invention can achieve an excellent release profile with the simple formulation described herein. Such additional excipients can increase or decrease the rate of release of the agent. Ingredients which can substantially increase the rate of release include pore forming agents and excipients which facilitate polymer degradation. For example, the rate of polymer hydrolysis is increased in non-neutral pH. Therefore, an acidic or a basic excipient such as an inorganic acid or inorganic base can

be added to the polymer solution, used to form the microparticles, to alter the polymer erosion rate.

A preferred embodiment of the described sustained release formulations consists essentially of the biocompatible polymer and naltrexone. By "consists essentially of" is meant the absence of ingredients which substantially increase the rate of release of the active agent from the formulation. Examples of additional excipients which would not be expected to substantially increase or decrease the rate of release of the agent include additional active agents and inert ingredients.

In yet another embodiment, the formulation consists of the biocompatible polymer and naltrexone. By "consists of" is meant the absence of components or ingredients other than those listed and residual levels of starting materials, solvents, etc. from the process.

As stated above, the formulation preferably releases naltrexone over a period of at least about one, two, three or four weeks. As such, the formulation can be administered using a dosing schedule which achieves the desired therapeutic levels for the desired period of time. For example, the formulation can be administered and, optionally, the patient monitored until levels of the drug being delivered return to baseline. Following an actual or projected return to baseline, the formulation can be administered again. Alternatively, the subsequent administration of the formulation can occur prior to achieving baseline levels in the patient. As such, the formulation can be advantageously administered weekly, with a one week release formulation, biweekly with a two week release formulation, or monthly with a four week release formulation. Vivitrex is a four week release formulation with a monthly (e.g., every four weeks) administration. The therapy can end after a single dose or can be maintained for longer periods of time. In one embodiment, the therapy can maintained for at least about 4, 8, 12, 16, 20 and 24 weeks or more. Where more than one administration is given, the second administration can be given 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 and combinations thereof. In this context "about" preferably means within three days of the targeted date.

Particularly good results were achieved upon administering the same formulation and same dose with each administration. Thus, where a 380 mg dose was given in the first administration, good to excellent results were achieved when the second and subsequent doses were about 380 mg. Surprisingly, good to excellent results were also obtained when each dose administered contained 190 mg naltrexone, particularly in men and women who were abstinent from alcohol in the three or five days prior to commencing treatment. As such, in one embodiment of the invention, the doses and/or formulations administered in each subsequent administration were similar or the same. As stated above, the formulation is preferably a microsphere formulation and is administered by IM injection. Administration to the buttock in a volume of up to about 4 mL in an injectable diluent was performed in the trials leading up to these inventions.

The methods of the inventions achieved good to excellent results in women and, in particular, men. Good to excellent results were achieved in young individuals (defined as less than 50 years of age), particularly men. Individuals afflicted by alcohol dependency, such as a heavy drinker achieved good to excellent results. A heavy drinker is understood in the art to include women who consume four or more alcoholic beverages in a day and men who consume five or more alcoholic beverages in a day.

In yet another embodiment, the inventions include 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 accordance with the protocols and/or dosing regimens described herein. In one embodiment, the increase in days prior to occurrence of alcohol consumption can include the consumption of a single alcoholic beverage or it can include consumption of four or five alcoholic beverages, such as the number of drinks characterizing an episode of "heavy drinking," above. In general, the greater the number of days that transpire prior to alcohol consumption indicates a more successful therapy.

EXEMPLIFICATION

Example 1

Method for Manufacturing Vivitrex® Long Acting Formulations

The invention includes a preferred method for manufacturing extended release devices, wherein the resulting device contains a mixture of the described polymorphic forms.

Polymer solution can be formed by dissolving a poly(lactide)-co-glycolide polymer, such as a 75:25 DL PLGA (poly(lactide)-co-glycolide) in a polymer solvent, such as ethyl acetate (EtAc), to form a solution. Preferred PLGA polymers are high molecular weight polymers, such as polymers possessing a molecular weight of at least about 100,000 daltons. A naltrexone solution can be formed by dissolving naltrexone base in a suitable solvent, such as benzyl alcohol (BA), to form a solution. The polymer solution and the naltrexone solution are preferably mixed together to form a drug/polymer solution that will be the "organic" or "oil" phase of the emulsion.

The "aqueous" or "continuous" phase of the emulsion (emulsifying solution) is prepared. The aqueous phase preferably contains poly(vinyl alcohol) (PVA) and polymer solvent, such as EtAc. The organic phase and the aqueous phase can be conveniently combined in a first static mixer to form an oil-in-water emulsion.

In an optional partial extraction step, the emulsion flows out of the first static mixer and into a second static mixer where the emulsion can be combined with a primary extraction solution which enters the second static mixer. The primary extraction solution (such as can be formed by an EtAc aqueous solution) can initiate solvent extraction from the microdroplets of the emulsion during the partial primary extraction step in the second static mixer.

The outflow of the first or second static mixer can flow into an extraction vessel containing primary extraction solution. The solvents (BA and EtAc) are substantially extracted from the organic phase of the emulsion in this primary solvent extraction step, resulting in nascent microparticles comprised mainly of polymer and drug. The primary solvent extraction step lasts for approximately six hours.

The microparticles can be collected, and vacuum dried, optionally with a nitrogen bleed using a customized vibratory sieve. After collection and prior to drying, the microparticles are rinsed with a 25% ethanol solution that removes the emulsifying agent (PVA), and enhances yield by aiding in the transfer of the microparticles to the cold dryer. This step is conducted, preferably at cold temperatures, until the desired level of dryness is achieved. As can be seen in the examples below, the degree of dryness (as measured, for example, by a humidity probe), impacts upon the degree of crystallinity achieved in the final product. For example, it can be advantageous to select a drying time of at least about 8, 16, 24 or 40 hours of drying. For example, it can be advantageous to select a drying time of at least about 8, 16, 24 or 40 hours where drying is 40%, 70%, 95% or 100% complete respectively. Drying is considered complete when the absolute humidity of the effluent gas reaches approximately 0 g/m^3.

The microparticles can then be resuspended in a second extraction solution. The second solution can contain the solvent desired to form the polymorphic form, such as ethanol. For example, a solution comprising at least about 10% by volume, preferably at least about 20% ethanol, can be used. This can be conveniently called the reslurry and secondary solvent extraction steps. The solvent, such as ethanol, can facilitate further extraction of BA and EtAc. Further, the crystallinity of the drug increases during the step. The secondary solvent extraction step is carried out in an extraction vessel for approximately two, three, four or more hours. This step can be conveniently completed at room temperature. However, other temperatures can be selected as well. In the collection/final dry step, the microparticles are collected, and vacuum dried with a nitrogen bleed using a customized vibratory sieve.

In the final harvest step, the microparticles can be transferred into a sterile container and stored, for example, in a freezer at -20°C, until filling into vials. Preferably, the stored microparticles are sieved through a 150 micron screen to remove any oversized material prior to filling into vials.

Preparation of naltrexone base microparticles.

The naltrexone base microparticles were produced using a co-solvent extraction process. The theoretical batch size was 15 to 20 grams. The polymer (MEDISORB®

7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6536 DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio.) 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 1/4" 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, 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 fifteen 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.

Preparation of naltrexone microspheres

A 1 kg batch of naltrexone microspheres was prepared as follows. Polymer solution was formed by dissolving 75:25 DL PLGA (poly(lactide)-co-glycolide) in ethyl acetate (EtAc) to form a solution of 16.7% polymer and 83.3% EtAc. A naltrexone solution was formed by dissolving naltrexone base in benzyl alcohol (BA) to form a solution of 30% naltrexone base anhydrous and 70% BA. The polymer solution and the naltrexone solution were mixed together to form a drug/polymer solution that was the "organic" or "oil" phase of the emulsion.

The "aqueous" or "continuous" phase of the emulsion (emulsifying solution) was prepared by dissolving poly(vinyl alcohol) (PVA) and EtAc in water-for-injection (WFI). The organic phase and the aqueous phase were combined in a first static mixer to form an oil-in-water emulsion. The droplet size of the emulsion was determined by controlling the flow rates of the two phases through the first static mixer.

In a partial primary extraction step, the emulsion flowed out of the first static mixer and into a second static mixer where the emulsion was combined with a Primary extraction solution which enters the second static mixer. The primary extraction solution (2.5% EtAc and 97.5% WFI at approximately 6°C) initiated solvent extraction from the microdroplets of the emulsion during the partial primary extraction step in the second static mixer.

The outflow of the second static mixer (combined flow stream of the emulsion and the primary extraction solution) flowed into an extraction vessel containing primary extraction solution. The solvents (BA and EtAc) were further extracted from the organic phase of the emulsion in this primary solvent extraction step, resulting in nascent microparticles comprised mainly of polymer and drug. The primary solvent extraction step lasted for approximately six hours.

The microparticles were collected, and vacuum dried with a nitrogen bleed using a customized vibratory sieve. After collection and prior to drying, the microparticles were rinsed with a 25% ethanol solution that removes the emulsifying agent (PVA), and enhances yield by aiding in the transfer of the microparticles to the dryer.

To further reduce the solvent levels the microparticles were resuspended in a second extraction solution of 25% ethanol and 75% WFI in the reslurry and secondary solvent extraction steps. The ethanol facilitated further extraction of BA and EtAc. The secondary solvent extraction step was carried out in an extraction vessel for approximately four hours. In the collection/final dry step, the microparticles were collected, and vacuum dried with a nitrogen bleed using a second customized vibratory sieve.

In the final harvest step, the microparticles were transferred into a sterile container and stored in a freezer at -20°C until filling into vials. Preferably, the stored microparticles were sieved through a 150 micron screen to remove any oversized material prior to filling into vials.

Example 2 Phase III Clinical Trial (also referred to herein as "ALK21-003")

Screening and Eligibility Criteria

Participants were male or nonpregnant, nonlactating female outpatients ≥ 18 years old with a current diagnosis of alcohol dependence. Patients had a minimum of two episodes of heavy drinking (≥5 alcoholic drinks/day for men and ≥4 drinks/day for women) per week during the 30 days prior to screening.

Exclusion criteria included evidence of liver failure; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than three times the upper limit of normal; history of pancreatitis; major depression with suicidal ideation, psychosis, or bipolar disorder (patients with treated depression and stable pharmacotherapy for at least 8 weeks were not excluded); dependence within the past year on benzodiazepines, opiates, or cocaine; more than 7 days of inpatient treatment for substance abuse during the month prior to screening; or use of opiates, oral naltrexone, or disulfiram during the two weeks prior to screening.

Detoxification prior to randomization was performed only if indicated by investigator judgment and had to be completed seven days before initiation of study therapy. Use of benzodiazepines was prohibited during the week prior to the first dose of study medication.

Randomization procedures

Patients were randomized to one of three treatment groups: long-acting injectable naltrexone 380 mg, long-acting injectable naltrexone 190 mg, or matching volumes of placebo (one-half of the placebo patients received an injection volume corresponding to 380 mg and the other half received an injection volume corresponding to 190 mg). The study used a dynamic randomization procedure to balance allocation on gender, patient-specified goal of total abstinence, self-reported abstinence for the 7-day period prior to first injection, and study site.

Study Procedures and Outcome Definitions

Patients received an injection of study medication at 4-week intervals over 24 weeks, alternating between the left and right gluteus maximus. Injections were prepared and administered by individuals who were not involved in any of the safety or efficacy assessments, and treatment assignment was blinded to all study personnel.

All patients received standardized supportive therapy (12 sessions) using the BRENDA model (Volpicelli JR, Pettinati HM, McLellan AT, O'Brien CP. *Combining medication and psychosocial treatments for addictions: the BRENDA approach.* New York: The Guilford Press; 2001), a six-stage low-intensity intervention designed to facilitate direct feedback with respect to addiction-related consequences. During this trial, BRENDA sessions were administered by study site personnel including psychologists, nurses, therapists, counselors, and physicians.

The number of standard drinks consumed per day was recorded using the Timeline Follow Back (TLFB) method (Sobell LC, Sobell MB. *Timeline Followback: a technique for assessing self-reported ethanol consumption*, In: Allen J, Litten RZ, eds. Measuring alcohol consumption: psychosocial and biological methods. Totowa, NJ: Humana Press, 1992:41-72). Breath alcohol levels of $\leq$0.02 gm/dL were required before self-report data were collected. Patients who discontinued study drug treatment prematurely were allowed to remain in the study, continue to follow the established visit and procedure schedule, and receive BRENDA treatment.

Study Formulation: Naltrexone long-acting injection (Vivitrex®) consists of microspheres (approximately 100 μM) composed of naltrexone and polylactide-co-

glycolide polymeric matrix (Medisorb®), a common biodegradable medical polymer with an extensive history of human use in absorbable sutures and extended-release pharmaceuticals. Following injection, naltrexone on the surface of the microspheres is released, yielding peak concentrations within three days. Thereafter, by a combination of diffusion and erosion, naltrexone is further released for greater than 30 days.

Definition of Outcomes. The primary efficacy endpoint was the event rate of heavy drinking over the 24 weeks of treatment. The definition of heavy drinking (≥5 drinks per day for men and ≥4 drinks per day for women) is consistent with that used in previous trials of oral naltrexone. Secondary endpoints included the event rate of "risky" drinking (>2 drinks per day for men and >1 drink per day for women) specified by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (U.S. Department of Agriculture/U.S. Department of Health and Human Services. Home and Garden Bulletin no. 232. *Nutrition and your health: dietary guidelines for Americans*. 3rd ed. Washington, DC: Supt. of Docs., U.S. Government. Printing Office, 1990), and the event rate of any drinking days. Secondary endpoints included median relapse to heavy drinking, NIAAA-derived "safe drinking" any drinking , and number of alcoholic drinks per day. Exploratory endpoints included serum gamma-glutamyl transferase (GGT) changes over time, and time to patient discontinuation. Adverse events were coded using the MedDRA dictionary of preferred terms.

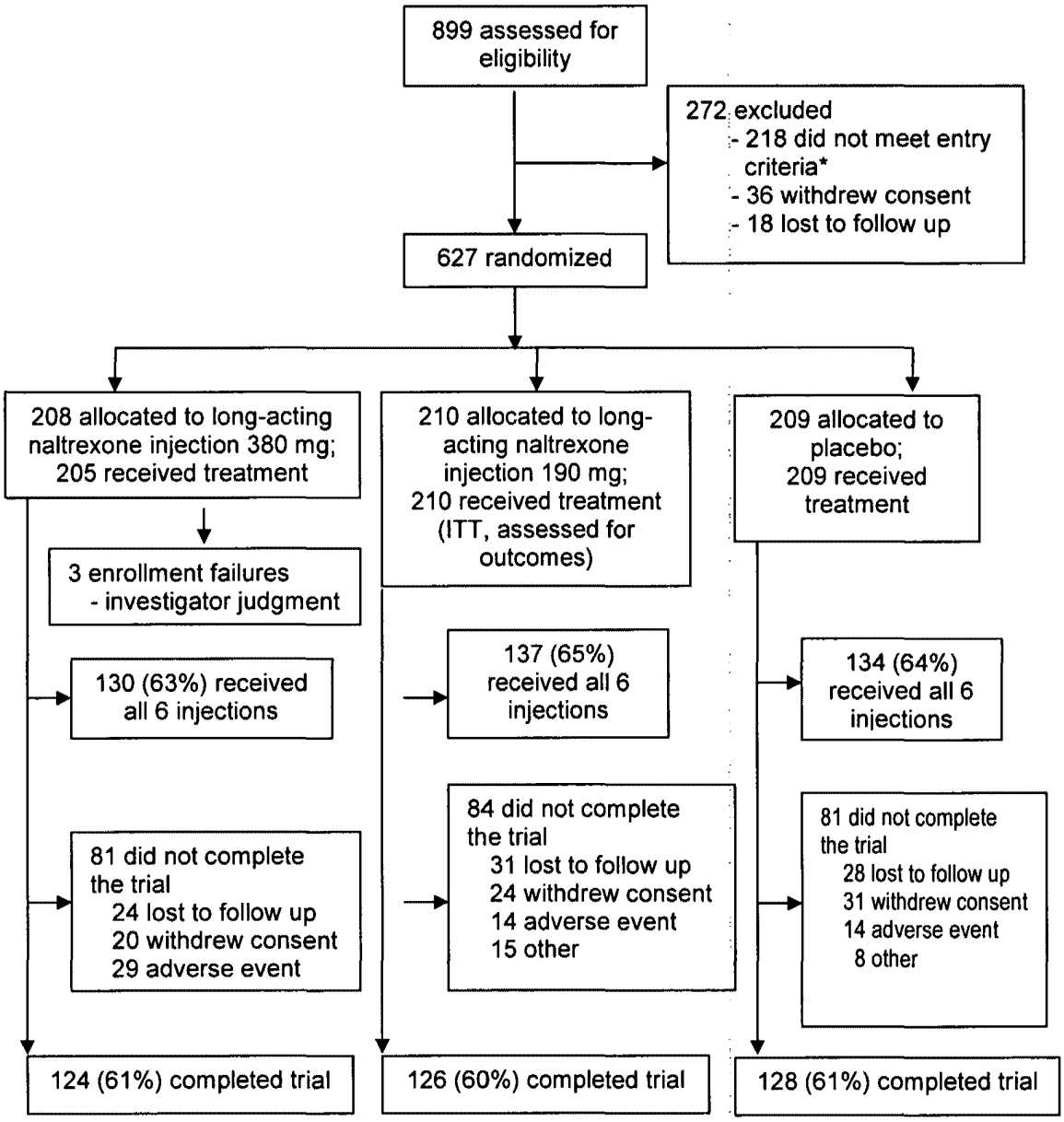
Statistical Methods

The primary analysis for the primary and secondary endpoints was performed on an intention-to-treat population (i.e., all randomized patients who received at least one dose of study medication). The primary objective was to determine whether treatment with long-acting naltrexone (at either 190 mg or 380 mg) decreased the event rate of heavy drinking relative to treatment with placebo injection. Statistical methods to analyze multiple drinking episodes in alcoholism treatment clinical trials have been described by Wang et al., Short of complete abstinence: an analysis exploration of multiple drinking episodes in alcoholism treatment trials. Alcohol Clin Exp Res. 2002; 26:1803-9. The primary analysis for the primary endpoint was performed using a stratified recurrent event Andersen-Gill like model with robust

variance estimation (Lin DY, Wei LJ, Yang I, and Ying Z. *Semiparametric regression for the mean and rate functions of recurrent events*. J Royal Stat Soc (B) 2000; 62: 711–30; SAS/STAT user's guide. Version 8. Cary, NC: SAS Institute, 1999:2596). The parameters estimated in the model were those representing the treatment effect of 190 mg relative to placebo and 380 mg relative to placebo. The analysis was performed on all heavy drinking events captured during the treatment period reflecting the days between first treatment and 30 days following the last dose of study medication. Analyses of the primary endpoint were performed by gender and for each of the other predefined stratification variables. Retention rates were evaluated by generating Kaplan-Meier curves for the time to study discontinuation. A log rank test was used to examine treatment group differences.

RESULTS

624 patients were randomly assigned and received treatment, constituting the intention-to-treat population for analyses, according to the flow chart below:



Patients were predominantly male (68%) and Caucasian (84%), with a mean age of 45 years (range 19-74). Baseline drinking averaged 20 (SD=8) heavy drinking days over the 30 days prior to study entry. Overall, 8.8% of patients were abstinent during the 7-day lead-in period and 43% of the patients had a goal of total abstinence. Pretreatment characteristics of the patients in the three treatment groups were similar (Table 1).

Table 1. Base-line characteristics of the patients (ITT population)

	Long-acting naltrexone 380 mg (N=205)			Long-acting naltrexone 190 mg (N=210)			Placebo (N=209)		
	Overall	Males	Females	Overall	Males	Females	Overall	Males	Females
Demographic and other variables									
Age (yr)	45.0±10.1	45.4±10.9	44.2±8.3	44.6±10.8	44.6±11.5	44.6±9.3	44.7±10.8	44.7±11.2	44.6±10.0
Gender			67			68		143	66
No. of patients (%)		138 (67.3)	(32.7)		142 (67.6)	(32.4)		(68.4)	(31.6)
Race or ethic group (%)									
White*	83.9	81.9	88.1	80.5	78.9	83.8	86.1	83.2	92.4
Weight (kg)*	84.2±20.7	90.5±19.2	71.1±17.5	82.7±19.8	88.7±19.2	70.5 15.3	81.6±17.0	86.1±15.5	71.9±16.2
Employment status									
(% employed ≥20 hr/week)	70.2	71.0	68.7	71.0	73.9	64.7	72.2	72.0	72.7
Current (%) smoker*	48.5	53.3	38.8	50.7	53.9	44.1	42.3	45.8	34.8
Current antidepressant use (%)*	30.2	21.7	47.8	26.3	21.3	36.8	29.2	24.5	39.4
Liver enzymes									
AST*†	30.0±13.1	32.5±14.3	24.7±8.0	32.7±17.4	35.7±18.6	26.4±12.5	31.9±18.1	33.8±18.5	27.7±16.5
ALT*†	31.9±19.2	37.3±20.5	20.8±8.6	32.9±20.6	38.2±22.1	21.8±10.9	34.0±21.8	38.1±22.4	25.0±17.6
GGT*	58.6±60.8	67.7±63.8	39.8±49.7	73.5±86.4	86.6±90.5	46.1±70.3	75.6±113.9	87.2±127.3	50.5±72.0
Goal of abstinence (%)	43.9	47.1	37.3	42.9	41.5	45.6	43.1	45.5	37.9
Heavy drinking days in 30 prior to first dose (%)	64.0±25.9	63.5±26.5	65.0±24.8	65.6±26.4	64.6±25.4	67.7±28.4	65.2±24.8	65.2±24.5	65.2±25.5
Abstinence for 7 days prior to first dose (%)	8.3	9.4	6.0	8.1	7.0	10.3	9.1	10.5	6.1
Self-help group attendance (%)*	11.7	13.0	9.0	10.5	12.0	7.4	11.0	13.3	6.1

Plus-minus values are mean ± standard deviation.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-Glutamyltransferase
*P > 0.05 (significant difference between men and women in the overall study population [N = 624]).
† The normal values for AST and ALT are gender and age specific:
ALT: Women 18-69 yr: 6-34 U/L, >69 yr: 6-32 U/L; Men 18-69 yr: 6-43 U/L, >69 yr: 6-35 U/L
AST: Women ≥18: 9-34 U/L; Men ≥18: 11-36 U/L

Overall, 401 patients (64%) received all 6 injections, and 378 patients (61%) completed the trial. Time to discontinuation was similar among groups. The median number of therapy sessions completed was 11 out of a maximum of 12 and 42.8% of patients attended all therapy sessions. The number of therapy sessions and the percentage of patients attending all sessions were similar among treatment groups.

Adverse events occurring in ≥10% of the patients during treatment with long-acting injectable naltrexone are listed in Table 2.

Table 2. Adverse events during treatment occurring in 10% or more of patients

Adverse Event, no. (%)	Long-acting naltrexone 380 mg (N=205)	Long-acting naltrexone 190 mg (N=210)	Placebo (N=209)
Nausea	70 (34%)*†	53 (25%)*	23 (11%)
Headache	46 (22%)	33 (16%)	34 (16%)
Fatigue	42 (21%)*	35 (17%)	23 (11%)
Insomnia	28 (14%)	27 (13%)	25 (12%)
Vomiting	28 (14%)*	22 (11%)	12 (6%)
Decreased appetite	26 (13%)*†	12 (6%)*	3 (1%)
Diarrhea	26 (13%)	23 (11%)	18 (9%)
Dizziness	26 (13%)*	23 (11%)*	8 (4%)
Nasopharyngitis	25 (12%)	32 (15%)	24 (12%)
Injection site pain	23 (11%)*	18 (9%)	12 (6%)
Upper respiratory tract infection	21 (10%)	15 (7%)	18 (9%)

* $P < 0.05$ vs placebo. † $P < 0.05$ vs Vivitrex 190 mg.
Note: Percentages are based on the number of patients in the ITT population (dosed at least once). Fischer's exact test used for association of treatment by adverse event; pair-wise comparisons with 2x2 tables.

Other adverse events, which occurred in less than 10% of subjects but more frequently in the long-acting naltrexone subjects ($P < 0.05$) included the following: abdominal pain, injection site induration, injection site pruritus, decreased libido, and arthralgia.

The most common adverse events were nausea, headache, and fatigue. Nausea was mild or moderate in approximately 95% of cases, the large majority of which occurred during the first month of treatment, with a median duration of 1 day. Nausea and decreased appetite occurred more frequently in patients treated with the long-acting naltrexone 380 mg.

Study discontinuation secondary to adverse events occurred in 14.1% (naltrexone 380 mg), 6.7% (naltrexone 190 mg) and 6.7% (placebo) of patients (P=0.013, 380 mg vs. 190 mg and placebo). The percentage of patients who experienced serious adverse events (SAEs) during treatment was similar among the treatment groups: 6.3% (n=13) for naltrexone 380 mg, 5.2% (n=11) for naltrexone 190 mg, and 7.2% (n=15) for placebo, with the most common SAE being hospitalization for alcohol detoxification. Two SAEs (eosinophilic pneumonia and interstitial pneumonia) were judged to be possibly related to study medication. Both events occurred in patients treated with naltrexone 380 mg and resolved with treatment. The most common injection site reaction was tenderness, occurring after 15.9% of 380 mg doses and 13.6% of 190 mg doses, and after 17.6% of high-volume placebo injections and 9.2% of low-volume placebo injections. Seven patients discontinued injections due to site reactions: 4 naltrexone 380 mg patients, 2 naltrexone 190 mg patients, and 1 high-volume placebo patient.

Mean AST and ALT levels, did not change significantly over the course of treatment or with medication. Furthermore, long-acting naltrexone was not associated with an increased rate of AST or ALT elevations above three times the upper limit of normal.

Analyses of primary and secondary efficacy variables measured during the 6-month treatment period are listed in Table 3.

Table 3. Analyses of Primary and Secondary Efficacy Outcomes

			Naltrexone 190 mg vs Placebo		Naltrexone 380 mg vs Placebo	
	Stratification Variable	**Population**	**Hazard Ratio (95% CI)**	**P value**	**Hazard Ratio (95% CI)**	**P value**
Primary Outcome						
Heavy Drinking	Overall Sample	Overall	0.83 (0.68, 1.02)	0.076	0.75 (0.60, 0.94)	0.025
	Gender	Male	0.75 (0.58, 0.95)	0.020	0.52 (0.38, 0.69)	<0.0001
		Female	1.05 (0.73, 1.51)	0.79	1.29 (0.91, 1.83)	0.31
	Goal of Total Abstinence	Yes	0.88 (0.61, 1.28)	0.50	0.72 (0.48, 1.08)	0.11
		No	0.91 (0.70, 1.18)	0.48	0.79 (0.59, 1.05)	0.01
	Lead-in Drinking	Yes	0.93 (0.75, 1.15)	0.48	0.79 (0.62,1.00)	0.05
		No	0.05 (0.02, 0.15)	<0.0001	0.20 (0.07, 0.62)	0.005
Secondary Outcomes						
"Risky" drinking	Overall Sample	Overall	0.93 (0.80, 1.08)	0.32	0.92 (0.80, 1.07)	0.30
	Gender	Male	0.86 (0.70, 1.04)	0.11	0.72 (0.58, 0.89)	0.002
		Female	1.04 (0.83, 1.31)	0.73	1.20 (0.97, 1.49)	0.094
Nonabstinent days	Overall Sample	Overall	0.93 (0.82, 1.06)	0.30	1.00 (0.88, 1.14)	0.98
	Gender	Male	0.93 (0.78, 1.09)	0.37	0.87 (0.73, 1.04)	0.12
		Female	0.95 (0.77, 1.16)	0.61	1.19 (0.98, 1.44)	0.081

*National Institute on Alcohol Abuse and Alcoholism–specified level of "risky drinking" is ≥2 drinks per day for men and one drink for woman.
Note: For the primary endpoint (heavy drinking), the Hochberg method was used to adjust multiple comparisons. As specified a priori, the secondary outcomes (drinking above the NIAAA-specified level of "risky" drinking and nonabstinent days) are included for informational purposes, and no adjustments were made.

Overall, patients treated with long-acting naltrexone 380 mg experienced approximately a 25% greater reduction in the rate of heavy drinking than placebo-treated patients (P<0.025) (Figure 1). The reduction in heavy drinking was greatest in men treated with naltrexone 380 mg (n=138), who showed a 48% greater reduction in the rate of heavy drinking than placebo-treated patients (n=143) (P<0.001). In contrast, no significant differences were observed between women treated with naltrexone 380 mg (n=67) and those receiving placebo (n=66).

Overall, patients treated with naltrexone 190 mg reported a 17% greater reduction in the rate of heavy drinking than placebo-treated patients (P=0.076). The effect of naltrexone 190 mg was more pronounced for men (n=142), who experienced approximately a 25% greater reduction in the rate of heavy drinking than placebo (n=143) (P=0.020). As with 380 mg, women treated with naltrexone 190 mg (n=68) showed no significant difference from placebo (n=66).

The other predefined stratification variables—goal of total abstinence and lead-in drinking—also influenced heavy drinking in the overall sample. Patients who had a goal of total abstinence (n = 270) experienced a 39% greater reduction in heavy drinking relative to patients who did not (n=354), and those who were abstinent during the week prior to treatment (n=53) had a 76% greater reduction in heavy drinking compared to those who drank during that week (n = 571). With respect to medication effects, the relative reduction in heavy drinking associated with the 380mg and the 190mg dose compared to placebo was similar whether or not participants had a goal of total abstinence as shown in Table 3. In contrast, the effect of treatment with the 380 mg dose and the 190mg dose relative to the placebo dose was most pronounced in the subgroup that was abstinent at randomization compared to the subgroup that was not abstinent (Table 3). However, this latter finding must be interpreted cautiously in light of the small sample size for the group with no lead-in drinking (n = 53).

Consistent with observed reductions in heavy drinking, there was a 15% reduction in GGT during the study compared to pretreatment for the overall sample. Men treated with long-acting naltrexone had a 20% and 24% reduction in GGT for the

380 mg and 190 mg groups, respectively, compared to 12% for placebo. No difference from placebo was seen in the women.

The rate of NIAAA "risky" drinking was not significantly lower with long-acting naltrexone in the overall sample but was significantly reduced (by 28%) in men who received injections of naltrexone 380 mg (see Table 3). No effect was shown on the rate of drinking days for the overall population or separately for men or women (Table 3).

During the treatment period, patients in all three groups demonstrated substantial reductions from their baseline levels of heavy drinking days. Figure 2 shows the change from baseline in the median number of heavy drinking days per month, by treatment group and gender.

This study enrolled a population of predominantly actively drinking patients, only 8.3% of whom were abstinent for the 7-day period prior to treatment. The number of patients who maintained complete abstinence during the trial was 7% in the naltrexone 380 mg group, 6% in the 190 mg naltrexone group, and 5% in the placebo group. The proportion of patients who experienced at least one heavy drinking day was 83% for naltrexone 380 mg, 86% for naltrexone 190 mg, and 89% for placebo. There were no significant group differences on either of these measures.

The median number of days to first heavy drinking event overall was 3 for the placebo group, 4 for the 190 mg group and 6 for the 380 mg group (Table 4). The difference between the 380 mg group and placebo was statistically significant (log rank test, P=0.0111). Evidence of more pronounced treatment effects were seen with Vivitrex suspension 190 mg and 380 mg in the subgroups of subjects who were abstinent 4 days prior to first study dose and those with no lead in drinking compared with the population overall.

To more comprehensively assess the effects of Vivitrex suspension, analyses of the secondary endpoints were also performed using the predefined subpopulation of subjects who had no lead-in drinking (abstinent during the 7 days immediately prior to randomization) and a larger subpopulation of subjects who were abstinent during the 4 days immediately prior to randomization. These subjects are most analogous to

subjects historically studied with oral naltrexone which generally required minimum 3 to 5 days of abstinence prior to randomization.

Table 4. Median Number of Days to Relapse to First Heavy Drinking Event

SUBGROUP	*PLACEBO*	*190 MG*	*380 MG*
ITT Population	*3*	*4*	*6**
Abstinent During the 4 Days Prior to Randomization	*20*	*47*	*181†*
No Lead-In Drinking (Abstinent During the 7 Days Prior to Randomization)	*29*	*>170*	*181*

* P=0.011, 380 mg compared with placebo

† P=0.042, 380 mg compared with placebo

DISCUSSION

The main findings of this study were that a long-acting, injectable formulation of naltrexone, in conjunction with psychosocial treatment, significantly reduced heavy drinking in a large, geographically varied sample of treatment-seeking patients with alcohol dependence. These findings were most evident in men, with the median male subject reporting 7% heavy drinking days at the 380 mg dose compared to 23% heavy drinking days with placebo. In addition, the efficacy of the 380 mg dose was evident within the first month after the initial injection, and was robust over the 180-day treatment period, irrespective of whether there was drinking in the week before the first injection or the patient's goal at treatment entry was total abstinence. Importantly, naltrexone injections were well tolerated, few serious adverse events were reported, and there was no evidence of hepatotoxicity.

The primary outcome measure in this study—heavy drinking—is the *sine qua non* of alcoholism, and is both clinically meaningful and of public health importance. Of the various measures of drinking behavior, heavy drinking shows the highest correlation with negative life consequences such as impaired driving, interpersonal problems, and injuries. Substantial reductions in heavy drinking, as seen among men treated with naltrexone 380 mg, can be expected to lead to improvements in various areas of health and in the quality of life.

Over the last decade, studies of oral naltrexone have yielded modest evidence of efficacy, which may explain, in part, why naltrexone has not been commonly used in the clinical management of alcoholism. The effectiveness of oral naltrexone may be undermined by patients stopping or skipping their doses. Therefore, the encouraging results from the present study using the long-acting 380 mg naltrexone formulation are likely to increase confidence among clinicians that a pharmacological option exists to treat alcohol dependence. Furthermore, this study enrolled subjects without an abstinence requirement. This is in contrast to the majority of prior studies which limited enrollment to subjects who had achieved short term abstinence.

This study is the first to examine prospectively the effect of gender on response to naltrexone. Results of the multiple-event rate analysis showed a clear advantage for naltrexone over placebo among men but not women. Nonetheless, the women in this trial reduced their heavy drinking substantially, irrespective of whether they received active medication. One possible explanation for the gender difference is that women may have received a greater therapeutic benefit from the psychosocial intervention. Further evaluation of factors that may explain the differential response in women is needed utilizing a sample that is large enough to yield adequate statistical power.

In addition, the pharmacokinetic profile of long-acting injectable naltrexone differs substantially from that of the oral formulation. Peak naltrexone levels and the generation of 6-β-naltrexol via first-pass metabolism may contribute to reduced tolerability of oral naltrexone. A long-acting injectable naltrexone formulation may mitigate these effects by both eliminating daily naltrexone peaks and decreasing the ratio of 6-β-naltrexol to the parent compound compared with oral treatment (Kranzler HR, Modesto-Lowe V, Nuwayser ES. *Sustained-release naltrexone for alcoholism treatment: a preliminary study.* Alcohol Clin Exp Res 1998; 22:1074-9; Verebey K, Volavka J, Mule SJ, Resnick RB: *Naltrexone: disposition, metabolism, and effects after acute and chronic dosing.* Clin Pharmacol Ther 1976; 20:315-28).

In summary, the results from this trial, one of the largest studies ever conducted to evaluate a medication for treatment of alcohol dependence, provide evidence that long-acting injectable naltrexone is a safe and effective medication for this indication,

particularly among men. This formulation should be a valuable addition to the treatments that are currently available for use in alcoholism rehabilitation.

Example 3

Comparison of Efficacy with Long-Acting Naltrexone injectable versus Oral Naltrexone

A comparison of efficacy between the long-acting naltrexone formulations of the invention and oral naltrexone was performed. As a direct head-to-head comparison of efficacy has not been studied, a definitive comparison of efficacy between Vivitrex and oral naltrexone cannot be made. Nevertheless, 3 recent meta-analyses of the efficacy with oral naltrexone (Srisurapanont M, Jarusuraisin N. *Opioid antagonists for alcohol dependence*. The Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD001867.pub2. DOI: 10.1002/14651858.CD001867.pub2. This version first published online: 24 January 2005 in Issue 1, 2005. Date of most recent substantive amendment: 05 November 2004; Bouza C, Magro A, Munoz A, Amate JM. *Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review*. Addiction. 2004 Jul; 99(7):811-828; Hopkins, John Sloan, Master Paper Presentation entitled: *Meta Analysis of Clincal Trials of Naltrexone and Acamprosate for the Treatment of Alcoholism- What does the evidence tell us?* UNC-CH Department of Epidemiology, presented at the Research Society for Alcoholism Annual Scientific Meeting, March 25, 2002) provide useful historical standards for a semi-quantitative comparison.

The most commonly used endpoint for oral naltrexone has been the dichotomous outcome, relapse to heavy drinking (yes/no). The studies of oral naltrexone have generally evaluated subjects who have been abstinent for 3-5 days over a 12-week treatment period. The corresponding endpoint and population; the rate of relapse to heavy drinking at 12 weeks in subpopulation of subjects in ALK21-003 Phase III clinical study who were abstinent during the 4 days immediately prior to randomization was therefore selected to compare to the results of oral studies.

In Hopkins (supra), a quantitative meta-analysis was undertaken, in which the oral naltrexone versus placebo risk differences for the dichotomous outcome—relapse to heavy drinking (yes or no)—were obtained from applicable studies. Nine studies were included. In the fixed effects model, the estimate of the combined risk difference was 0.13 (13%) with 95% confidence interval (0.08, 0.17). This result suggested a treatment effect favoring oral naltrexone.

In ALK21-003, there were 56 subjects dosed (28 placebo, 28 Vivitrex 380 mg) who were abstinent for 4 days prior to receiving study drug. At 12 weeks, the relapse rate was 11/28 (0.39) in the Vivitrex 380 mg treatment group compared with 20/28 (0.71) in the placebo group. The risk difference (95% CI) in this subset of subjects is 0.32 (32%) with a 95% confidence interval (0.08, 0.58). The result with Vivitrex suspension thus compares favorably with the overall risk difference determined by Hopkins in a similar subject population.

In the Cochrane analysis (*supra*), the outcome, relapse to heavy drinking, was also used as the endpoint in the meta-analysis. Instead of the risk difference, results are described in terms of the relative risk (RR). At 12 weeks, oral naltrexone significantly decreased the relapse rate by 36% relative to placebo (RR [95% CI] = 0.64 [0.51, 0.82]). Using the relapse rates described above for the subjects who were abstinent during the 4 days prior to randomization in the ALK 21-003 study, Vivitrex suspension 380 mg significantly decreased the relapse rate by 45% relative to placebo (RR [95% CI] = 0.55 [0.33, 0.92]).

Bouza, et al, *supra*, report the reduction of the relapse rate of their meta analysis of short term studies (≤12 weeks) in terms of the odds ratio [OR, (95% CI): 0.62, (0.52,0.75)]. This analysis indicated that the odds of relapsing to heavy drinking in subjects treated with oral naltrexone decreased 38% relative to placebo. Using the relapse rates previously described above for the applicable subjects in the ALK21-003 study the reduction of the relapse rate odds ratio is [OR, (95% CI): 0.26, (0.08,0.79)]. The odds of relapsing to heavy drinking of subjects treated with Vivitrex suspension 380 mg decreased 74% relative to placebo.

Table 5. Comparison of Results in ALK21-003 and 3 Published Meta-Analyses of Oral Naltrexone

	ALK21-003* 380 mg vs placebo	**Hopkins et al oral vs placebo**	**The Cochrane Review oral vs placebo**	**Bouza, et al oral vs placebo**
Risk difference (95% CI)	0.32 (0.08, 0.58) (32% reduction)	0.13 (0.08, 0.17) (13% reduction)	--	--
Relative risk (95% CI)	0.55 (0.33, 0.92) (45% reduction)	--	0.64 (0.51, 0.82) (36% reduction)	--
Odds ratio (95% CI)	0.26 (0.08, 0.79) (74% reduction)	--	--	0.62 (0.52, 0.75) (38% reduction)

* Based on results of the ALK21-003 study as described in the ALK21-003 final CSR.

Based on semi-quantitative comparisons to these 3 meta-analyses, the efficacy of Vivitrex suspension compares favorably with oral naltrexone.

Example 4

Effect of Long-Acting Injectable Naltrexone on Quality of Life

Objective: Assess the effect of long-acting injectable naltrexone (LA-NTX) on health-related quality of life (QoL) in patients with alcohol dependence.

Method: A 24-week, multicenter, double-blind, placebo-controlled study evaluated the safety and efficacy of LA-NTX, a polylactide microsphere intramuscular formulation of naltrexone given monthly. DSM-IV alcohol-dependent patients (N=624) were randomized to 6 monthly injections of LA-NTX 380 mg, LA-NTX 190mg, or placebo in combination with psychosocial support (BRENDA, see Volpicelli, *infra*). QoL was assessed using SF-36v2.0 (see Ware, *infra*).

Results: Baseline SF-36 Mental Component Scores (MCS) were 38.7, 40.3, and 40.6 for the 380mg, 190mg, and placebo groups, respectively (significantly lower than US population norms. Following treatment, MCS increased by 7.9, 6.2, 6.0, in the 380mg, 190mg, and placebo groups. The change from baseline was significant for all treatment groups ($P<0.001$) and was greater with 380mg vs. placebo ($P<0.05$). Improvements correlated positively with reduction in alcohol consumption. Physical Component Scores (normal at baseline for all groups) did not change with treatment.

Conclusion: A large sample of alcohol-dependent patients demonstrated deficits in mental health-related QoL, which improved significantly with treatment for alcohol dependence. LA-NTX plus psychosocial therapy showed improvements in QoL that were greater than treatment with psychosocial therapy alone.

Example 5

Durability of Effect of Long-acting Injectable Naltrexone

Objective: To assess the durability of effect and tolerability of long-acting injectable naltrexone (LA-NTX) in a 1-year extension study in patients with alcohol dependence.

Methods: A 24-week, multicenter, double-blind, placebo-controlled study evaluated the safety and efficacy of LA-NTX, a polylactide microsphere intramuscular formulation of naltrexone. DSM-IV alcohol-dependent patients (N=624) were randomized to 6 monthly injections of LA-NTX 380mg, LAN-TX 190mg, or placebo in combination with psychosocial support (BRENDA, Volpicelli et al., *Combining medication and pshychosocial treatments for additions: the BRENDA approach.* New York: The Guilford Press; 2001). 61% of patients completed the study, of whom 85% (N=332) enrolled in a 1-year open-label extension. Alcohol intake was recorded in the base and extension studies by the Timeline Followback method (Ware *et al., How to score version 2 of the SF-36®*, Lincoln RI: QualityMetric Incorprated; 2000).

Results: Patients randomized to 380mg in the base study continued to receive 380mg in the extension study (N=115). Mean percent heavy drinking days was similar in the base study (22.7%) and the extension (19.6%) study (*P*=NS). Patients treated with BRENDA and placebo injections who were switched to 380mg in the extension (N=60) showed significant reduction in percent heavy drinking days ($P<.01$). Once-monthly injections of LA-NTX were well tolerated.

Conclusions: Reduction in alcohol intake observed with LA-NTX and BRENDA during a 24-week double-blind study were durable and maintained during a 1-year open-label extension study.

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or

unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. 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. A method of treating an individual in need of naltrexone comprising administering a 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. 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. The method of Claim 3 wherein the naltrexone is administered in a long acting formulation comprising naltrexone.

5. 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. A method of treating an individual in need of naltrexone comprising administering a 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 days, such as within ten days, before said administration.

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

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

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

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

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

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

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

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

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

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

18. The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency, such as a heavy drinker.

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

20. The method of claim 1 wherein naltrexone is administered by injection, such as intramuscularly or subcutaneously.

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

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

24. The use of naltrexone in the manufacture of a long acting formulation for use in the methods of any one of the preceding claims.

25. A method for treating an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone to the individual in the absence of concomitant psychosocial treatment of the individual.

NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

ABSTRACT OF THE DISCLOSURE

The inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone. As such, 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 and to the use of naltrexone in the manufacture of medicaments for use in such methods.

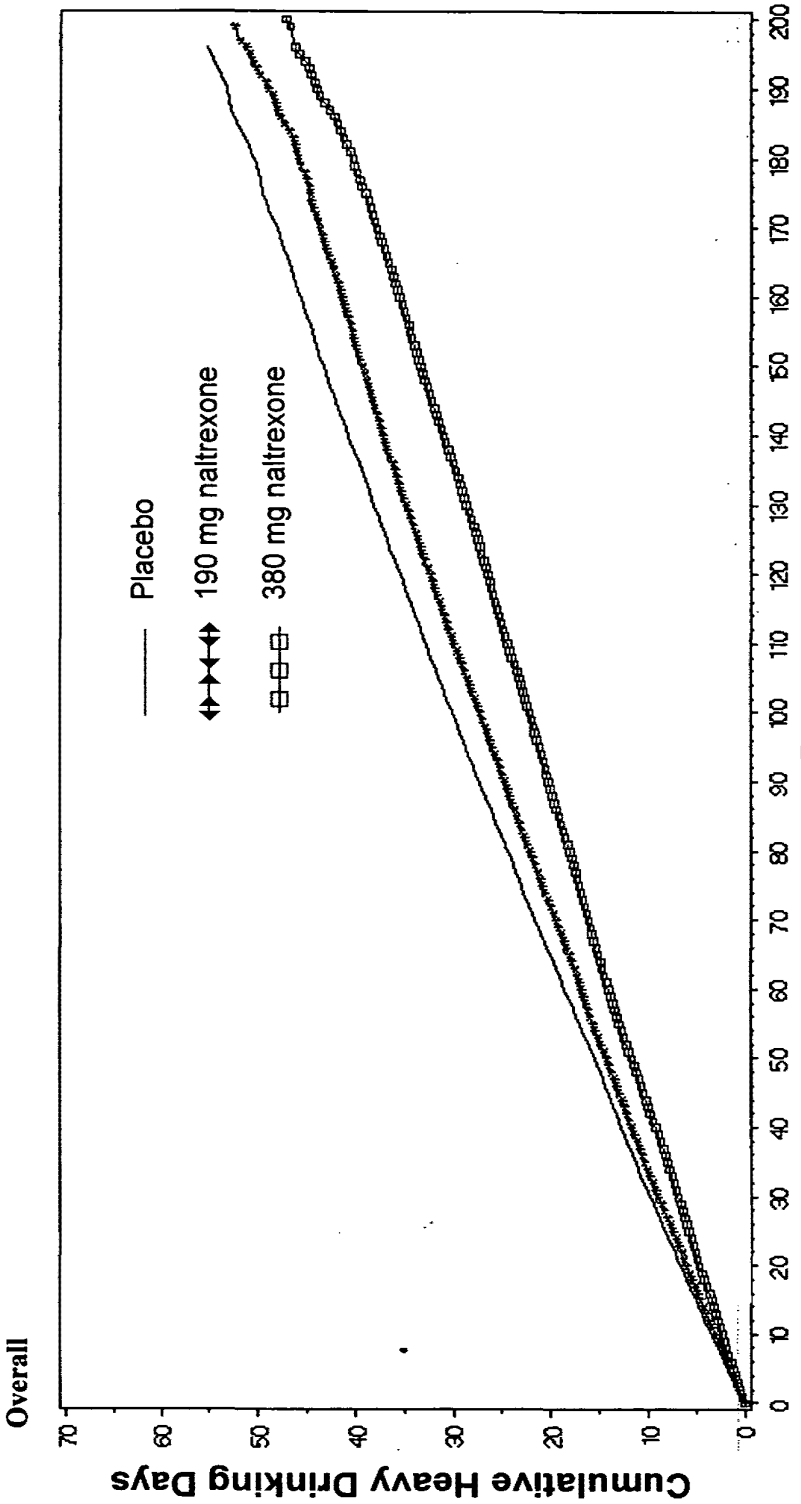

Overall
Cumulative Heavy Drinking Days
0
10
20
30
40
50
60
70
Days
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
Placebo
190 mg naltrexone
380 mg naltrexone

FIG. 1A

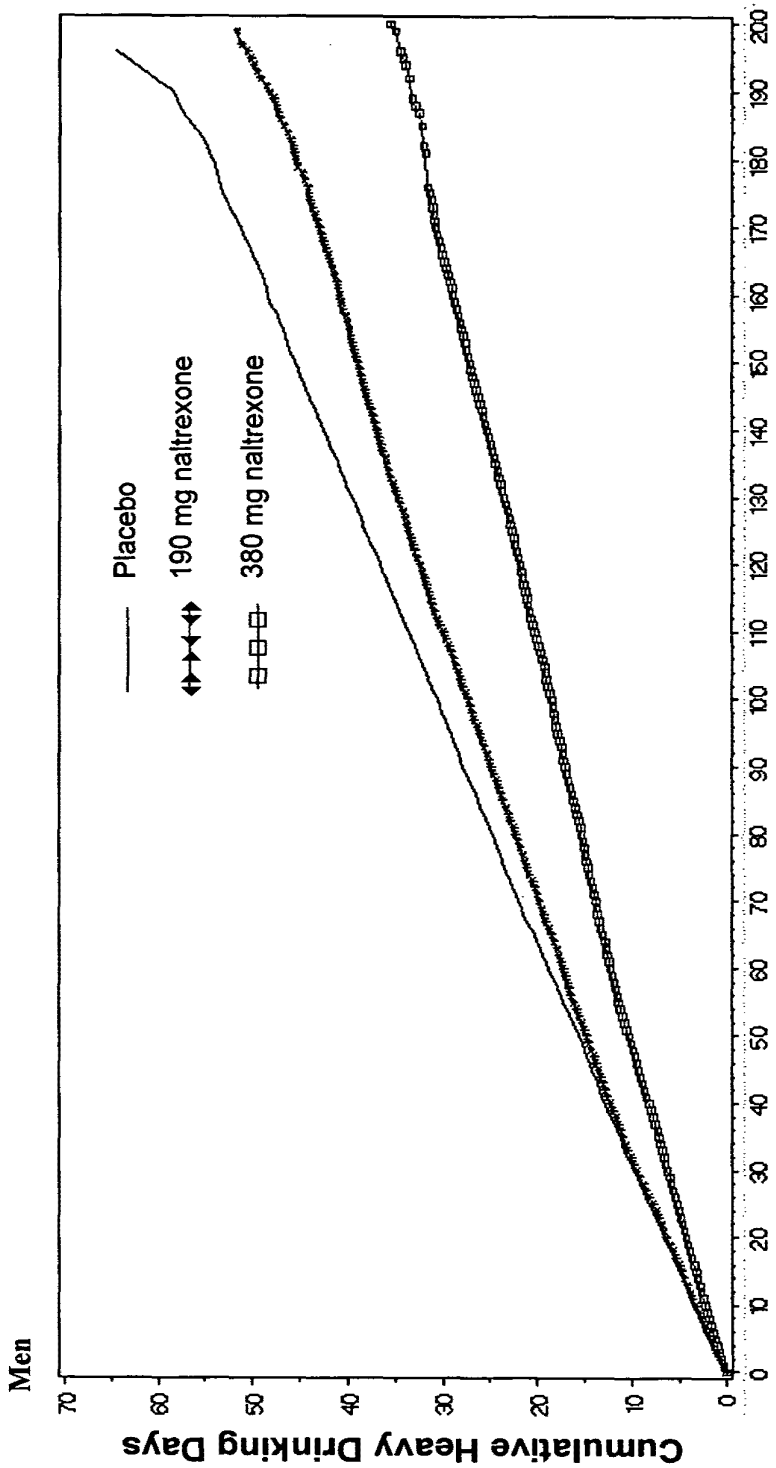

Men
Cumulative Heavy Drinking Days
Days
Placebo
190 mg naltrexone
380 mg naltrexone
0
10
20
30
40
50
60
70
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

FIG. 1B

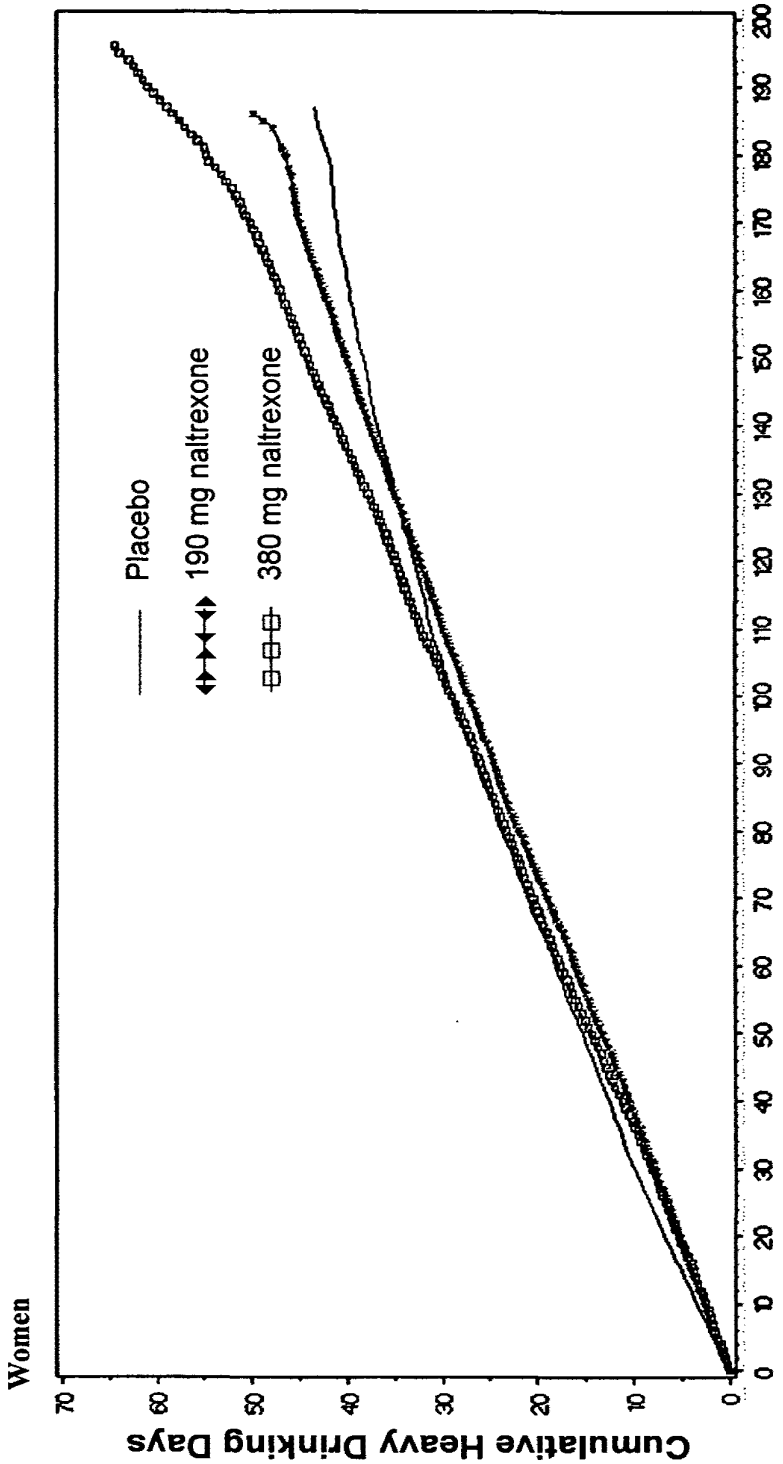

Women
Cumulative Heavy Drinking Days
0
10
20
30
40
50
60
70
Days
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
Placebo
190 mg naltrexone
380 mg naltrexone

FIG. 1C

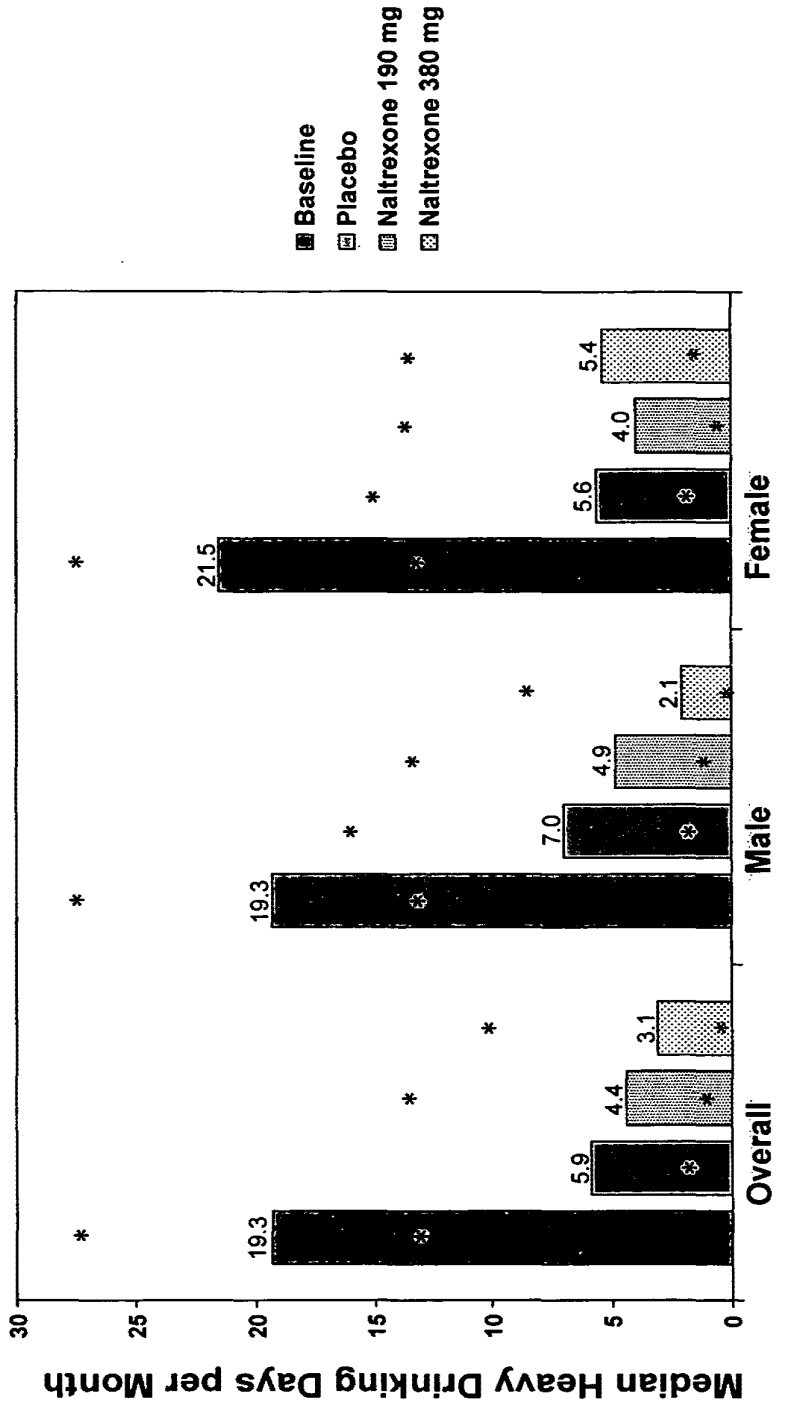

Baseline
Placebo
Naltrexone 190 mg
Naltrexone 380 mg
Median Heavy Drinking Days per Month
0
5
10
15
20
25
30
Overall
Male
Female
19.3
5.9
4.4
3.1
19.3
7.0
4.9
2.1
21.5
5.6
4.0
5.4

FIG. 2

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

11083167

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	25	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	25 minus 20=	* 5
INDEPENDENT CLAIMS	7 minus 3 =	* 4
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐			OR	OTHER THAN SMALL ENTITY	
RATE	FEE			RATE	FEE
BASIC FEE	150.00		OR	BASIC FEE	300.00
X$ 25=			OR	X$50=	250
X100=			OR	X200=	800
+180=			OR	+360=	
TOTAL			OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

1 2 3 5 6 20 25

SMALL ENTITY			OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE			RATE	ADDITIONAL FEE
X$ 25=			OR	X$50=	
X100=			OR	X200=	
+180=			OR	+360=	
TOTAL ADDIT. FEE			OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. 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.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

03/22/2005 EFLORES 00000070 11083167

01 FC:1011	300.00	OP
02 FC:1111	500.00	OP
03 FC:1311	200.00	OP
04 FC:1201	800.00	OP
05 FC:1202	250.00	OP

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/59033

Large

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

11/083167

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	25	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	47 minus 20=	* 27
INDEPENDENT CLAIMS	6 minus 3 =	* 3
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
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BASIC FEE		OR	BASIC FEE	300
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X100=		OR	X200=	600
+180=		OR	+360=	360
TOTAL		OR	TOTAL	2610

500
200

CLAIMS AS AMENDED - PART II

AMENDMENT A

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Independent	*	Minus	***	=
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AMENDMENT B

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Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

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AMENDMENT C

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Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

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X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. 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.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

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Adjustment date: 04/15/2005 UEDUVIJE
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04/15/2005 UEDUVIJE 00000035 502807 11083167

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04/15/2005 UEDUVIJE 00000036 502807 11084537

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PTO-1556
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*U.S. Government Printing Office: 2002 — 466-267/60033

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