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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/225,741	09/13/2005	Chih-Ming Chen	141-596 B	3874

47888 7590 12/04/2008

HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
12/04/2008	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.

Interview Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	MICAH-PAUL YOUNG	1618	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MICAH-PAUL YOUNG*. (3)_____.

(2) *Martin Endres*. (4)_____.

Date of Interview: *02 December 2008*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The Application has been abandoned*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/MICAH-PAUL YOUNG/ Examiner, Art Unit 1618	

Notice of Abandonment	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	MICAH-PAUL YOUNG	1618	

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

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *29 April 2008*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/MICAH-PAUL YOUNG/
Examiner, Art Unit 1618

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

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Office Action Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	MICAH-PAUL YOUNG	1618	

-- 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 ____ 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 _____.

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) _____ 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) _____ 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

Acknowledgment of Papers Received: Amendment/Response dated 2/6/08

Claim Rejections - 35 USC § 103

1. 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.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 43-78, 80 and 82-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over the disclosures of Elger et al (USPN 4,834,985 hereafter '985). The claims are drawn to a controlled release oral dosage form comprising a metformin in a matrix with a controlled release carrier and a controlled release coating.

4. The '985 patent discloses a controlled release formulation comprising metformin (col. 3, lin. 9), various carriers (col. 4, lin. 54-69) and a coating (col. 5, lin. 23-28, example 9). Regarding claim 75, the '985 patent discloses that the formulation can be granulated into individual granules/pellets or microparticles comprising the active agents and a carrier polymer constituting multiple dosage forms (col. 5, lin. 20-27). Regarding claim 77, the '985 patent

discloses that the dosage from comprises binders such as polyvinylpyrrolidone (example 17). Regarding claim 78, the '985 patent discloses that the dosage from comprises components used as absorption enhancers such as various polyethylene glycols and cetostearyl alcohol (examples). Regarding claim 80 which recite specific carrier polymers, the '985 patent discloses that the dosage form comprises cellulose ethers such as hydroxypropylcellulose (col. 2, lin. 24-33).

5. Regarding the specific dissolution profile recited in the claims, it is the position of the Examiner that such limitations are functional and same compositions must have the same properties. The limitations of claims 43-74 are encompassed inherently by the disclosures of the '985 patent. The configuration of the carrier polymers, concentration of the drug present in the core and the presence of a membrane coating determine the dissolution profile. The tablets of the '985 patent disclose each of these components. Further these components can be modified in order to achieve a desired release rate. For disorders that require faster acting active agents, the carrier materials can be chosen and provided in the proper concentrations to achieve a faster or slower release. In the instant case 0-30% of the drug is to be released at a 2-hour mark with a plasma concentration of 1500 ng/ml. The compositions of the '985 patent can be configured to release 0-27% at the 2 hour mark with a plasma concentration of approximately 1600 ng/ml (examples and table 12). However through routine experimentation these dissolution profiles can be altered. It is the position of the Examiner that the dissolution profiles of the instant claims are obvious variations and can be determined through routine experimentation. For these reasons dissolution profile limitation do not impart patentability on the claims.

6. Regarding the Cmax values recited in the claims, it is the position of the Examiner that such limitations are functional and same compositions must have the same properties. These

limitations are seen as future intended uses for known formulations. Further, the claims recite that they are based on varying concentrations of the metformin, meaning the Cmax values are hypothetical at best. It is the position of the Examiner that any formulation matching the physical components as that of the instant claims, namely a metformin compound in a matrix with a controlled release carrier would be capable of achieving these Cmax values, and would inherently achieve these values. Also the claims recite that the formulation only be suitable for once-a-day administration, which is again a future intended use for the formulation. Any formulation can be made suitable for any type of administration. It is the position of the Examiner that such a limitation does not impart patentability.

7. Specifically regarding the Cmax values that are dependent on a specific hypothetical release concentration, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

8. With these things in mind it would have been obvious to follow the suggestions of the '985 patent in order arrive at the controlled release formulation of the instant claims. It would have been obvious to produce a controlled release formulation as disclosed in the '985 patent

with an expected result of a tablet useful in treating various disorders including serum glucose regulation.

9. Claims 43-88 rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Elger et al (USPN 4,834,985 hereafter '985) in view of Chen et al (USPN 5,837,379 hereafter '379). The claims are drawn to a controlled release dosage form comprising a passageway through the membrane and a plasticizer.

10. As discussed above the '985 patent obviates many aspects of the instantly claimed invention. The reference is silent however to a specific passageway out of the membrane coating or a specific plasticizer. These components are however well known in the art and would be obvious additions to the formulation of the '985 patent. They can bee seen in the '379 patent.

11. The '379 patent discloses a controlled release formulation comprising various active agents combined with controlled release carriers in a matrix surrounded by a membrane coating (abstract). The carrier polymers include cellulose ethers such as hydroxypropylcellulose (col. 4, lin. 25-30). The formulation further includes a plasticizer such as rapeseed oil, triacetin and glycerol sorbitol (col. 5, lin. 44-55). The formulation includes absorption enhancers such as sodium lauryl sulfate (examples) and binders such as povidone (examples). The formulation includes an opening in the membrane through which the core active agents are released (col. 3, lin. 50-60). The active agents include chlorporpamide a commonly associated compound useful in reducing serum glucose levels (col. 2, lin. 60). It would have been obvious to include the passageway forming polymers into the coating of the '985 patent in order to provide an improved for prolonged release of the active agents.

12. It would have been obvious to include the plasticizers and passageway-forming polymers of the '379 patent into the formulation of the '985 patent in order to maintain the integrity of the coating while releasing a steady stream of active agent over a longer period of time. It would have been obvious to one of ordinary skill in the art to combine the disclosures as such with an expected result of a sustained release composition capable of reducing serum glucose levels over an extended period of time.

Response to Arguments

Applicant's arguments filed 2/6/08 have been fully considered but they are not persuasive. Applicant argues that:

a. The '985 patent alone or in combination does not teach or suggest the "unique" *in vitro* or *in vivo* properties taught in the instant claims.

b. The combination of the '985 and '379 patent do not obviate the claims since the '379 patent does not overcome the deficiencies of the '985 patent and does not teach or suggest the "unique" *in vitro* or *in vivo* properties taught by the instant claims.

Regarding argument a., it remains the position of the Examiner that the '985 patent continues to obviate the claims. Applicant argues that the '985 patent does not disclose the "unique" release profile however it remains the position of the Examiner that as long as the formulation is capable for performing or achieving the desired result the '985 patent would read on the instant claims. In order for the formulation to be capable of the release profile it must meet the compositional limitations of the claims. By meeting the compositional limitations of

the formulation the compound of the prior art would inherently be capable of the "unique" *in vivo* or *in vitro* properties. The claims recite a controlled release formulation comprising metformin, a controlled release carrier, and a controlled release coating. The '985 patent discloses a controlled release matrix formulation comprising the same drug, combined with the same controlled release carriers and controlled release coating materials as the instant claims. Since a composition and its properties cannot be separated and the composition of the '985 patent is fundamentally the same as the instant claims, the formulation must have the same release profile. Applicant argues that the '985 patent does not disclose the unique physical, or metabolic properties of metformin that must be considered when making a controlled release formulation. These considerations would have been obvious to one of ordinary skill in the art and are the definition of routine experimentation. The '985 patent provides a wide range of active ingredients all with their specific formulating parameters, and it remains the potion of the Examiner that the modification and appreciation of the specific formulating parameters for each active compound would be well within the level of skill in the art and obvious to one of ordinary skill in the art. For these reasons the claims remain obviated.

Regarding argument b., it remains the position the Examiner that the combination of the '985 and the 379 patent obviates the claims. As discussed above the '985 patent meets the compositional limitations of the instant claims, and thereby would also meet the inherent release characteristics as well. The reference however is silent to the specific plasticizer or passageway through the surrounding membrane. The '379 patent provides these components, establishing the level of skill in the art. The '985 patent disclose the use of a plasticizer, though different than that of the instant claims. The '379 patent provides the specific compound. It would have been

obvious to include them into the '985 patent in order to provide a more precise release rate or modify it completely. These modifications would have been obvious to one of ordinary skill in the art since the '985 and '379 patents provide similar carrier formulations comprising cellulose ethers, and active compound useful in treating patients with NIDDM. For these reasons the composition of the combination would have obviated the instant claims.

Conclusion

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

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICAH-PAUL YOUNG whose telephone number is (571)272-0608. The examiner can normally be reached on Monday-Friday 7:00-4:30; every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on 571-272-0616. 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.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/MICAH-PAUL YOUNG/
Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 11/225,741	Applicant(s)/Patent Under Reexamination CHEN ET AL.	
	Examiner MICAH-PAUL YOUNG	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,834,985	05-1989	Elger et al.	424/488
*	B	US-5,837,379	11-1998	Chen et al.	424/465
	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
	11225741	CHEN ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

✓	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	04/21/2008								
	1	-								
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CLAIM		DATE								
Final	Original	04/21/2008								
	37	-								
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	04/21/2008								
	73	✓								
	74	✓								
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	88	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11225741	CHEN ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

SEARCHED

Class	Subclass	Date	Examiner
424	464, 469, 450, 484	12/8/05	MPY
514	414, 415		
above	to date	6/17/06	
above	to date	2/27/07	
above	to date	9/25/07	
above	to date	4/18/08	MPY

SEARCH NOTES

Search Notes	Date	Examiner
east brs search, all databases searched odp with 11/224,784	12/8/05	MPY
search updated 6/21/06, 2/27/07, odp with 11/224,784 and 10/796, 411		
search updated 9/25/07 and 4/18/08 odp droppped with abn of copending apps	4/18/08	

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

OIPE IAP78
FEB 06 2008
PATENT & TRADEMARK OFFICE

Docket No. 141-596B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Chen et al.

Serial No.: 11/225,741 Group Art Unit: 1618

Filed: September 13, 2005 Examiner: Micah Paul Young

For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

New York, New York 10036
February 4, 2008

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

AMENDMENT

Sir:

In response to the Office Action dated October 2, 2007, in the above-identified application, Applicants respectfully request amendment and reconsideration.

In accordance with the provisions of 37 C.F.R. § 1.121 attached hereto on separate sheets are: a) an amendment to the claims and b) a remark section.

I hereby certify that this paper or fee is being deposited with the United States Postal Service as first class mail on **February 4, 2008** in an envelope addressed to:

Commissioner for Trademarks
P.O. Box 1451
Alexandria, VA 22313-1451

Martin P. Endres, Reg. No. 35,498

02/06/2008 CCHAU1 00000021 11225741
02 FC:1202 350.00 OP

AMENDMENTS TO THE CLAIMS

Please amend claims 43 and 47 as indicated below.

Please add new claims 82-88.

A complete list of claims as currently amended follows:

1-42 (cancelled).

43. (currently amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; ~~and~~ (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients and (iii) providing a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

44. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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45. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

46. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

47. (currently amended)) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-25 ~~0-30~~% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C.; ~~and~~ (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients and (iii) providing a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

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48. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

49. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

50. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

51. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

52. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

53. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin

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therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

54. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

55. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

56. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

57. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

58. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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59. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

60. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

61. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

62. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

63. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

64. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin

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therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

65. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

66. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

67. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

68. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

69. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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70. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

71. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 17200 ng·hr/ml to about 33900 ng·hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

72. (previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 8600 ng·hr/ml to about 16950 ng·hr/ml upon administration of a 1000 mg once-a-day dose of metformin.

73. (previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 12900 ng·hr/ml to about 25425 ng·hr/ml upon administration of a 1500 mg once-a-day dose of metformin.

74. (previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 21500 ng·hr/ml to about 42375 ng·hr/ml upon administration of a 2500 mg once-a-day dose of metformin.

75. (previously presented) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

76. (previously presented) The controlled release oral dosage form of claim 43, comprising a core comprising said metformin or pharmaceutically acceptable salt

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thereof and a membrane surrounding said core said membrane comprising the controlled release carrier.

77. (previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises a binding agent.

78. (previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises an absorption enhancer.

79. (previously presented) The controlled release oral dosage form of claim 76, further comprising a passageway in the membrane.

80. (previously presented) The controlled release oral dosage form of claim 76, wherein said controlled release carrier comprises a polymer selected from the group consisting of cellulose esters, cellulose diesters, cellulose trimesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate and cellulose acetate butyrate.

81. (previously presented) The controlled release oral dosage form of claim 80, wherein said membrane further comprises a plasticizer.

82. (new) The controlled release dosage form of claim 43 wherein the mean time to maximum plasma concentration (Tmax) is 5.5 to 7.5 hours.

83. (new) The controlled release dosage form of claim 47 wherein the mean time to maximum plasma concentration (Tmax) is 5.5 to 7.5 hours.

84. (new) The controlled release dosage form as defined in claims 82 wherein the dosage form is administered at dinner time.

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85. (new) The controlled release dosage form as defined in claim 83 wherein the dosage form is administered at dinner time.

86. (new) The controlled release dosage form as defined in claim 43 wherein the width at 50% of the height of a mean plasma concentration/time curve of the metformin is from about 5.5 to about 10 hours.

87. (new) The controlled release dosage form as defined in claim 86 wherein the width at 50% of the height of a mean plasma concentration/time curve of the metformin is from about 6 to about 8 hours.

88. (new) The controlled release dosage form as defined in claim 47 wherein the width at 50% of the height of a mean plasma concentration/time curve of the metformin is from about 6 to about 8 hours.

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REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 43-88 are in the present application.

On pages 6 and 7 of the Office Action, the Examiner provisionally rejected claims 43-76 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-20 and 28-30 of co-pending Application Serial No. 10/796,411 and over claims 43-73 of co-pending Application No. 11/224,784.

Applicants respectfully submit that these rejections are moot because both cited Applications have been abandoned. Attached hereto as Exhibits A and B for the Examiner's convenience, are the Notice of Abandonment for Application Serial Nos. 10/796,411 and 11/224,784, respectively.

On page 2 of the Office Action, the Examiner rejected claims 43-78 and 80 under 35 U.S.C. § 103(a) in view of Elger et al., United States Patent No. 4,834,985 (the '985 patent).

On page 5 of the Office Action, the Examiner rejected claims 43-81 under 35 U.S.C. § 103(a) in view of the '985 patent and Chen et al., United States Patent No. 5,837,379 (the '379 patent).

In response to these rejections, Applicants have amended independent claims 43 and 47 to add an additional *in vivo* limitation. More specifically, claim 43 has been amended to indicate that the dosage form exhibits an *in vivo* plasma concentration curve wherein the width at 50% height of the mean plasma concentration is about 4.5 to about

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13 hours. Claim 47 has been amended to indicate that the dosage form exhibits an *in vivo* plasma concentration curve wherein the width at 50% height of the mean plasma concentration is about 5.5 to about 10 hours. No new matter is added by these amendments. Support can be found on page 5, lines 15-17 of the specification. Applicants have also amended the *in vitro* dissolution element of claim 47 to recite that 0-25 of the metformin is released after 2hours. No new matter is added by these amendments and support can be found on page 6, lines 18-23 and page 19, lines 5-15 of the specification.

Applicants have also added new claims 82-88 which further require the dosage from to exhibit a specific Tmax of 5.5 to 7.5 hours, be administered at dinner time and to further refine the 50% width of the mean plasma concentration time curve. No new matter is added by these amendments and support can be found on page 7, lines 15-18; page 7, line 27 to page 8, line 2; and page 5, lines 15-18 of the specification.

The currently amended claims describe a metformin dosage form that exhibits a very beneficial plasma profile. More specifically, the recited dosage form will exhibit an *in vivo* release of metformin that has a maximum concentration of metformin that is skewed to the earlier portion of the 24 hours dosing period (i.e., an asymmetrical plasma concentration time curve) and will result in peak metformin plasma concentration levels that do not increase adverse events associated with immediate release metformin. In addition, the width of the plasma concentration at 50% height insures that the metformin drug level will rise and fall in the earlier portion of the dosing period. Applicants have discovered that this rise and fall in the earlier portion of the time curve allows the dosage form to be administered at dinner time resulting in the maximum amount of metformin

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being present in a patient's blood when most needed, i.e., during the period of glucogenesis. See page 7, line 27 to page 8, line 2 of the specification. The release and shape of the claimed metformin dosage form is not typical for a controlled release dosage form which seeks to provide constant blood levels of drug and a uniform or symmetrical shape to the plasma concentration time curve that is centered on the middle of the dosing period.

With respect to the rejection of the claims, Applicants respectfully submit that the currently amended claims are patentable over the '985 patent alone or combined with the '379 patent.

The '985 patent teaches a specific type of controlled release dosage form that releases the drug over an extended period of time and will "**maintain** drug level in the blood or target tissue within the therapeutic range for 8 hours of more". Col. 1, lines 10-13 (emphasis added). The dosage form taught by the '985 patent is a matrix comprising a polydextrose or cyclodextrin and a fatty alcohol or polyalkylene glycol. Col. 1, lines 28-34. The '985 patent provides no guidance for preparing a controlled release metformin composition with the unique *in vitro* and *in vivo* properties recited in the pending claims. The '985 patent only mentions metformin in a long laundry list of possible drugs. It does not address any of the unique chemical, physical or metabolic properties of metformin that need to be considered when developing a controlled release metformin product.

Further, the only *in vivo* data disclosed in the '985 patent confirms that the '985 patent is concerned with maintaining constant drug levels rather than providing maximum metformin to a patient when most needed. More specifically, Table 12

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appearing on Col. 15, lines 55-65 of the '985 patent reports the mean plasma theophylline concentrations over a single twenty-four hour dosing period. The maximum concentration reported in Table 12 is 3.0 μg/ml which occurs at 7 and 8 hours and therefore the 50% height would occur at 1.5 μg/ml. Using the data provided in Table 12, the width at 50% height would be at least 20 hours. This value is much greater than the 4.5 to 13 hours required by the pending claims.

Because the presently claimed dosage form recites a unique combination of *in vitro* and *in vivo* properties that are specifically designed to deliver the maximum amount of metformin to a patient at the time when it is most needed and not to just maintain metformin levels as taught by the '985 patent, it is respectfully submitted that the present claims are patentable over the '985 patent.

The '379 patent fails to overcome the deficiencies of the '985 patent. Like the '985 patent, the '379 patent teaches a specific controlled release dosage form designed to maintain therapeutic drug levels over time. See generally: Col. 3, line 15 ("The unitary core osmotic tablet of the invention which contain nifedipine as the medicament has been demonstrated to have bioequivalent pharmacokinetic performance (i.e. **maintain** a sustained 24 hour drug plasma levels)". (emphasis added). The pharmacokinetic data reported in the '379 patent confirms the maintenance teaching. Figure 1 of the '379 patent is the mean plasma concentration curve for Procardia XL® (a commercially available controlled release nifedipine product) and a controlled release nifedipine product prepared according to the examples of the '379 patent. A quick analysis of Figure 1 of the '379 patent shows the width at 50% height is at least 20 hours. This width at 50% height

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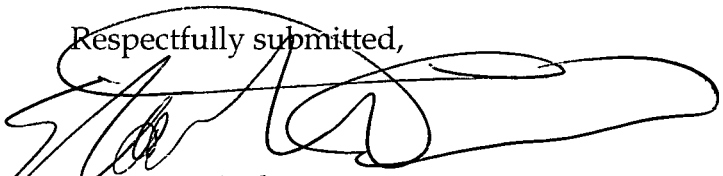
taught by the '379 patent is well outside the 4.5 to 13 hours recite in the pending claims.

Because neither the '985 patent nor the '379 patent disclose or suggest to an individual of ordinary skill a controlled release dosage form that exhibits a width at 50% height of about 4.5 to about 13 hours as required by the pending claims, it is respectfully submitted that the pending claims are patentable over the cited references.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,411	03/09/2004	Chih-Ming Chen	300.1005 CON	9033

7590 10/11/2007

DAVIDSON, DAVIDSON & KAPPEL, LLC
14th Floor
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EXAMINER
YOUNG, MICAH PAUL

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/11/2007	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.

Notice of Abandonment	Application No.	Applicant(s)	
	10/796,411	CHEN ET AL.	
	Examiner	Art Unit	
	Micah Paul Young	1618	

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

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *05 February 2007*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

Applicant's representative was contacted on October 3, 2007 to confirm that no response was filed.

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/224,784	09/13/2005	Chih-Ming Chen	300.1005CON4	4024

47888 7590 11/19/2007

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EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
11/19/2007	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.

AUROBINDO EX. 1017, 36

Notice of Abandonment	Application No.	Applicant(s)	
	11/224,784	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

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

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *02 April 2007*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

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PTO/SB/22 (10-07)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2006** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 141-596B
Application Number 11/225,741	Filed September 13, 2005
For CONTROLLED RELEASE METFORMIN COMPOSITIONS	
Art Unit 1618	Examiner Micah Paul Young

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

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

		Fee	Small Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$120	$60	$ $120.00
☐	Two months (37 CFR 1.17(a)(2))	$460	$230	$
☐	Three months (37 CFR 1.17(a)(3))	$1050	$525	$
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

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

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

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

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

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-1540. I have enclosed a duplicate copy of this sheet.

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

I am the

☐ applicant/inventor.

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

☑ attorney or agent of record. Registration Number 35,498

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

Signature	February 4, 2008 Date
Martin P. Endres Typed or printed name	212-302-8989 Telephone Number

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

☐ Total of _____ forms are submitted.

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

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02/06/2008 CCHAU1 00000021 11225741 120.00 OP
01 FC:1251

OIPE 1AP78 FEB 06 2008 PATENT & TRADEMARK OFFICE

PTO/SB/21 (09-06)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chen et al.
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	141-596B

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Return Receipt Postcard
Check for $470.00

Remarks

Check is for a 1-month extension of time fee ($120.00) and the fee for seven (7) new dependant claims.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Martin P. Endres		
Date	February 4, 2008	Reg. No.	35,498

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or 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 on the date shown below:

Signature			
Typed or printed name	Martin P. Endres	Date	February 4, 2008

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OIPE MAR 18
FEB 06 2008
PATENT & TRADEMARK OFFICE

PTO/SB/17 (10-07)
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2008

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 470.00

Complete if Known	
Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chen et al.
Examiner Name	Micah Paul Young
Art Unit	1618
Attorney Docket No.	141-596B

METHOD OF PAYMENT (check all that apply)

☑ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 08-1540 Deposit Account Name: _____

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

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	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)	210	105
Multiple dependent claims	370	185

Total Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 20 or HP =	7	x 50	= 350.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

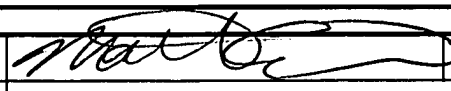
If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets	Number of each additional 50 or fraction thereof		Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 = _____	(round **up** to a whole number) x	_____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1-month Extension of time	120.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 35,498	Telephone 212-302-8989
Name (Print/Type)	Martin P. Endres		Date Februay 4, 2008

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PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/225,741	09/13/2005	

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	02/06/2008	(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))	* 46	Minus	** 39	= 7	X $ =		OR	X $50=	350
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $210=	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	**350**

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:
/EVELYN G. NIMMONS/

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/225,741	09/13/2005	Chih-Ming Chen	141-596 B	3874

47888 7590 10/02/2007

HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
10/02/2007	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.

AUROBINDO EX. 1017, 42

Office Action Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

-- 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 *23 July 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) *43-81* 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) *43-81* 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment of Papers Received: Response dated 7/9/07.

Claim Rejections - 35 USC § 103

1. 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.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 43-78 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over the disclosures of Elger et al (USPN 4,834,985 hereafter '985). The claims are drawn to a controlled release oral dosage form comprising a metformin in a matrix with a controlled release carrier and a controlled release coating.

4. The '985 patent discloses a controlled release formulation comprising metformin (col. 3, lin. 9), various carriers (col. 4, lin. 54-69) and a coating (col. 5, lin. 23-28, example 9). Regarding claim 75, the '985 patent discloses that the formulation can be granulated into individual granules/pellets or microparticles comprising the active agents and a carrier polymer constituting multiple dosage forms (col. 5, lin. 20-27). Regarding claim 77, the '985 patent

discloses that the dosage from comprises binders such as polyvinylpyrrolidone (example 17). Regarding claim 78, the '985 patent discloses that the dosage from comprises components used as absorption enhancers such as various polyethylene glycols and cetostearyl alcohol (examples). Regarding claim 80 which recite specific carrier polymers, the '985 patent discloses that the dosage form comprises cellulose ethers such as hydroxypropylcellulose (col. 2, lin. 24-33).

5. Regarding the specific dissolution profile recited in the claims, it is the position of the Examiner that these limitations do not impart patentability to the claims. The limitations of claims 43-74 are encompassed inherently by the disclosures of the '985 patent. The configuration of the carrier polymers, concentration of the drug present in the core and the presence of a membrane coating determine the dissolution profile. The tablets of the '985 patent disclose each of these components. Further these components can be modified in order to achieve a desired release rate. For disorders that require faster acting active agents, the carrier materials can be chosen and provided in the proper concentrations to achieve a faster or slower release. In the instant case 0-30% of the drug is to be released at a 2-hour mark with a plasma concentration of 1500 ng/ml. The compositions of the '985 patent can be configured to release 0-27% at the 2 hour mark with a plasma concentration of approximately 1600 ng/ml (examples and table 12). However through routine experimentation these dissolution profiles can be altered. It is the position of the Examiner that the dissolution profiles of the instant claims are obvious variations and can be determined through routine experimentation. For these reasons dissolution profile limitation do not impart patentability on the claims.

6. Regarding the Cmax values recited in the claims, it is the position of the Examiner that such limitations do not impart patentability on the claims. These limitations are seen as future intended uses for known formulations. Further, the claims recite that they are based on varying concentrations of the metformin, meaning the Cmax values are hypothetical at best. It is the position of the Examiner that any formulation matching the physical components as that of the instant claims, namely a metformin compound in a matrix with a controlled release carrier would be capable of achieving these Cmax values, and would inherently achieve these values. Also the claim recite that the formulation only be suitable for once-a-day administration, which is again a future intended use for the formulation. Any formulation can be made suitable for any type of administration. It is the position of the Examiner that such a limitation does not impart patentability.

7. Specifically regarding the Cmax values that are dependent on a specific hypothetical release concentration, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

8. With these things in mind it would have been obvious to follow the suggestions of the '985 patent in order arrive at the controlled release formulation of the instant claims. It would

have been obvious to produce a controlled release formulation as disclosed in the '985 patent with an expected result of a tablet useful in treating various disorders including serum glucose regulation.

9. Claims 43-81 rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Elger et al (USPN 4,834,985 hereafter '985) in view of Chen et al (USPN 5,837,379 hereafter '379). The claims are drawn to a controlled release dosage form comprising a passageway through the membrane and a plasticizer.

10. As discussed above the '985 patent obviates many aspects of the instantly claimed invention. The reference is silent however to a specific passageway out of the membrane coating or a specific plasticizer. These components are however well known in the art and would be obvious additions to the formulation of the '985 patent. They can bee seen in the '379 patent.

11. The '379 patent discloses a controlled release formulation comprising various active agents combined with controlled release carriers in a matrix surrounded by a membrane coating (abstract). The carrier polymers include cellulose ethers such as hydroxypropylcellulose (col. 4, lin. 25-30). The formulation further includes a plasticizer such as rapeseed oil, triacetin and glycerol sorbitol (col. 5, lin. 44-55). The formulation includes absorption enhancers such as sodium lauryl sulfate (examples) and binders such as povidone (examples). The formulation includes an opening in the membrane through which the core active agents are released (col. 3, lin. 50-60). The active agents include chlorporpamide a commonly associated compound useful in reducing serum glucose levels (col. 2, lin. 60). It would have been obvious to include the

passageway forming polymers into the coating of the '985 patent in order to provide an improved for prolonged release of the active agents.

12. It would have been obvious to include the plasticizers and passageway-forming polymers of the '379 patent into the formulation of the '985 patent in order to maintain the integrity of the coating while releasing a steady stream of active agent over a longer period of time. It would have been obvious to one of ordinary skill in the art to combine the disclosures as such with an expected result of a sustained release composition capable of reducing serum glucose levels over an extended period of time.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 43-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,4-20 and 28-30 of copending Application

No. 10/796,411. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to controlled release formulation of metformin comprising a matrix core comprising controlled release carrier polymers, absorption enhancers, and binders. A membrane comprising a plasticizer and at least one passageway through the membrane surrounds the matrix core. The claims of each recite a specific release profile and in vitro properties that would be inherent to the formulation. If issued these claims would act as intervening art over one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 43-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-73 of copending Application No. 11/224,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to controlled release formulation of metformin comprising a matrix core comprising controlled release carrier polymers, absorption enhancers, and binders. A membrane comprising a plasticizer and at least one passageway through the membrane surrounds the matrix core. The claims of each recite a specific release profile and in vitro properties that would be inherent to the formulation. If issued these claims would act as intervening art over one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Micah-Paul Young whose telephone number is 571-272-0608. The examiner can normally be reached on M-F 6:00-3:30 every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. 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.

Micah-Paul Young
Examiner
Art Unit 1618

MP Young

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Notice of References Cited	Application/Control No. 11/225,741	Applicant(s)/Patent Under Reexamination CHEN ET AL.	
	Examiner Micah-Paul Young	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,834,985	05-1989	Elger et al.	424/488
*	B	US-5,837,379	11-1998	Chen et al.	424/465
	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
11/225,741	CHEN ET AL.
Examiner	**Art Unit**
Micah-Paul Young	1618

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	9/12/07
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/225,741	CHEN ET AL.	
Examiner	**Art Unit**	
Micah-Paul Young	1618	

SEARCHED			
Class	Subclass	Date	Examiner
424	464, 469,450, 484	12/8/2005	MPY
514	414,415		
above	to date	6/17/2006	
above	to date	2/27/2007	
above	to date	9/25/2007	

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
east br search all databses odp with 11/224,784	12/8/2005	MPY
search updated 6/21/06 and 2/27/07 odp with 11/224,784 & 10/796,411		

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	ATTY. DOCKET NO./TITLE
11/225,741	09/13/2005	Chih-Ming Chen	141-596 B

CONFIRMATION NO. 3874

OC000000025040260

47888
HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

Date Mailed: 07/26/2007

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/17/2007.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

EA

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
OFFICE COPY

OIPE IAP92 JUL 17 2007 PATENT & TRADEMARK OFFICE

IFW

PTO/SB/21 (09-06)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chen et al.
Art Unit	1618
Examiner Name	Micah Paul Young
Total Number of Pages in This Submission: 3	Attorney Docket Number: 141-596 B

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☑ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  Statement Under 37 CFR 3.73 (b)
  Return Receipt Postcard

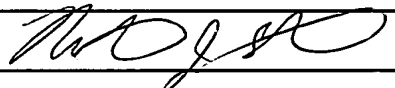
Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Matthew J. Solow		
Date	July 13, 2007	Reg. No.	56,878

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or 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 on the date shown below:

Signature			
Typed or printed name	Matthew J. Solow	Date	July 13, 2007

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 2 hours 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/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
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POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chen et al.
Title	Controlled Release Metformin Compositions
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	141-596 B

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 47888

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:

☑ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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	Roberta Loomar	Date	7-12-07
Name	Roberta Loomar	Telephone	954-762-6211
Title and Company	Vice President, Chief Compliance Officer and Assistant General Counsel; Andrx Corporation		

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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OIPE IAP92 JUL 17 2007 PATENT & TRADEMARK OFFICE

PTO/SB/96 (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Chih-Ming Chen et al.

Application No./Patent No.: 11/225,741 Filed/Issue Date: September 13, 2005

Entitled: CONTROLLED RELEASE METFORMIN COMPOSITIONS

Andrx Labs, LLC (Name of Assignee), a Limited Liability Company (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 follows:

1. From: Chih-Ming Chen et al. To: Andrx Corporation
The document was recorded in the United States Patent and Trademark Office at
Reel 011679, Frame 0517, or for which a copy thereof is attached.

2. From: Andrx Corporation, A Florida Corporation To: Andrx Corporation, A Delaware Corporation
The document was recorded in the United States Patent and Trademark Office at
Reel 013792, Frame 0227, or for which a copy thereof is attached.

3. From: Andrx Corporation To: Andrx Labs, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 013788, Frame 0187, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[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, to record the assignment 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.

Roberta Loomar	July 12, 2007
Signature	Date
Roberta Loomar	954-762-6211
Printed or Typed Name	Telephone Number
Vice President, Chief Compliance Officer and Assistant General Counsel	
Title	

This collection of information is required by 37 CFR 3.73(b). 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 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Docket No. 300-1005CON2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Chen et al.

Serial No.: 11/225,741 Group Art Unit: 1618

Filed: September 13, 2005 Examiner: Micah Paul Young

For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

New York, New York 10036
July 9, 2007

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

AMENDMENT

Sir:

In response to the Office Action dated March 7, 2007, in the above-identified application, Applicants respectfully request amendment and reconsideration.

This application was recently transferred from the firm of Davidson, Davidson & Kappell, LLC to Hedman & Costigan P.C. A substitute power of attorney will be submitted shortly.

In accordance with the provisions of 37 C.F.R. § 1.121 attached hereto on separate sheets are: a) an amendment to the claims and b) a remark section.

AMENDMENTS TO THE CLAIMS

Please amend claims 72-74 as indicated below.

A complete list of claims as currently amended follows:

1-42 (cancelled).

43. (previously presented) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

44. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

45. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from

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about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

46. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

47. (previously presented) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C.; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

48. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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49. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

50. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

51. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

52. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

53. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

54. (previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (C_{max}) of metformin

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therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

55. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

56. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

57. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

58. (previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

59. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

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60. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

61. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

62. (previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

63. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

64. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

65. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin

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therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

66. (previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

67. (previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

68. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

69. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

70. (previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (C_{max}) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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71. (previously presented) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 17200 ng·hr/ml to about 33900 ng·hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

72. (currently amended) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 8600 ng·hr/ml to about 16950 ng·hr/ml upon administration of a 1000 mg once-a-day dose of metformin.

73. (currently amended) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 12900 ng·hr/ml to about 25425 ng·hr/ml upon administration of a 1500 mg once-a-day dose of metformin.

74. (currently amended) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24\ hr}$ of metformin from about 21500 ng·hr/ml to about 42375 ng·hr/ml upon administration of a 2500 mg once-a-day dose of metformin.

75. (previously presented) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

76. (previously presented) The controlled release oral dosage form of claim 43, comprising a core comprising said metformin or pharmaceutically acceptable salt thereof and a membrane surrounding said core said membrane comprising the controlled release carrier.

77. (previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises a binding agent.

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78. (previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises an absorption enhancer.

79. (previously presented) The controlled release oral dosage form of claim 76, further comprising a passageway in the membrane.

80. (previously presented) The controlled release oral dosage form of claim 76, wherein said controlled release carrier comprises a polymer selected from the group consisting of cellulose esters, cellulose diesters, cellulose trimesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate and cellulose acetate butyrate.

81. (previously presented) The controlled release oral dosage form of claim 80, wherein said membrane further comprises a plasticizer.

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REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 43-81 are in the present application.

During preparation of the present response, Applicants noted a typographical error in claims 72-74. Specifically,the recited AUC values employed an incomplete unit of measurement. Claims 72-74 have been amended to correct this typographical error. No new matter is added. Support can be found on page 6, lines 5-11 of the specification.

In the Office Action, the Examiner provisionally rejected claims 43-76 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46 and 52-54 of copending Application Serial No. 11/224,785.

Applicants respectfully submit that this rejection is moot because copending Application Serial No. 11/224,785 has been abandoned.

In the Office Action, the Examiner also rejected claims 43-81 under 35 U.S.C. § 102(a) and (e) in view of United States Patent No. 6,099,862 (the '862 patent).

In response to this rejection, applications respectfully request reconsideration. First, all the pending claims are limited to a dosage form that consists of metformin or a pharmaceutically acceptable salt as the active agent and a controlled release carrier. Stated another way the claims are limited to a dosage form that provides for the controlled release of metformin or a pharmaceutically acceptable salt of metformin only.

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The '862 patent cannot anticipated the pending claims because the '862 patent requires the dosage form to provide for the controlled release of two different active ingredients, preferably metformin HCl and glipizide. See Col. 2, lines 38-52; Col. 5, lines 1-45 and figure 1 and 2. There is no disclosure in the '862 patent of a dosage form providing for the controlled release of metformin or a salt of metformin alone. Because the cited reference requires the controlled release of two separate and distinct drugs and the present claims are limited to the controlled release of only one drug, it is respectfully submitted that all the elements of the present claims are not disclosed specifically or inherently by the cited reference.

Applicants also respectfully submit that the '862 patent is not a proper reference under 35 U.S.C. § 102(a) or (e). 35 U.S.C. § 102(a) requires that the "invention" was "known or used by others" and 35 U.S.C. § 102(e) requires that the "invention" was described in a patent or an application of "another". The '862 patent does not meet the criteria of these sections because the present application and the '862 patent lists the same four individuals as inventors. In addition, at the time the present application was filed, the present application and the '862 patent were ultimately owned by the same entity, Andrx Corporation. Support for these factual assertions can be found in Exhibits A and B which are copies to the declaration executed by the inventors in the '862 patent and the present application respectively[1]. Also attached hereto as Exhibit C and D are copies of

[1] The declaration for the '862 patent lists the residence of Joseph Chou as 5755 N.W. 54th Place, Coral Springs, Florida and the declaration in the present application identifies Joseph Chou's residence as Manassas, VA. Subsequent to the invention of both the invention described in the '862 patent and the present application, but before filing of the present application, Joseph Chou retired from Andrx and moved to Manassas, VA.

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the recorded assignment for the '862 patent and the present application[2]. In light of the forgoing representations and Exhibit A-D, it is respectfully submitted that United States Patent No. 6,099,862 is not prior art under 35 U.S.C. § 102 (a) or (e).

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

Martin P. Endres
Reg. No. 35,498

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on July 9, 2007
Martin Endres

[2] The recorded assignment of the '862 patent identifies the assignee as Andrx Pharmaceuticals, Inc. Andrx Pharmaceuticals, Inc. was a wholly owned subsidiary of Andrx Corporation the assignee of the present application.

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OIPE IAP20
JUL 12 2007
PATENT & TRADEMARK OFFICE

Docket No.: 141-153

APPLICATION FOR UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY, AND PETITION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the invention which is described and which is claimed in the specification, entitled: CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE.

The specification [x] is attached hereto [ ] was filed on _____, as Application Serial No. _____.

I hereby state that I have reviewed and understand the contents of the specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.*

COUNTRY	APPLICATION NUMBER	DATE (DAY-MONTH-YEAR)	PRIORITY CLAIMED UNDER 35 USC§119
			YES [ ] NO [ ]
			YES [ ] NO [ ]

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Codes, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT International filing date of this application.

* In Non-Convention cases, a listing of all filings and current status of cases filed more than a year before the U.S. filing is required to comply with 37 CFR 1.56(a). Such a listing may be attached.

APPLICATION SERIAL NO.	FILING DATE	STATUS

I hereby appoint my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith:

Edward A. Hedman, Reg. No. 22,120; Thomas M. Gibson, Reg. No. 24,638; James V. Costigan, Reg. No. 25,669; Kenneth F. Florek, Reg. No. 33,173; Alan B. Clement, Reg. No. 34,563 and Martin P. Endres, Reg. No. 35,498, as my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

CORRESPONDENCE AND CALLS TO: James V. Costigan, Esq.
HEDMAN, GIBSON & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
Telephone: (212) 302-8989

The undersigned declares further that all statements made herein of his 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.

INVENTOR(S)	DATE	RESIDENCE AND P.O. ADDRESS
Name: Chih-Ming CHEN Signature:	Date: 8/23/98 Citizen of: USA	10680 S.W. 40th Manor Davie, FL 33328 USA
Name: Xiu Xiu CHENG Signature:	Date: 8/24/98 Citizen of: P.R. China	3150 W. Rolling Hills Circle Apt. 506 Davie, FL 33328 USA
Name: Joseph CHOU Signature:	Date: 8/24/98 Citizen of: USA	5755 N.W. 54th Place Coral Springs, FL 33067 USA

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Name: Steve JAN Signature:	Date: 8/26/98 Citizen of: USA	512 N.W. 120th Drive Coral Springs, FL 33071 USA

OIPE JUL 12 2007 PATENT & TRADEMARK OFFICE

Docket No. 300.1005

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: CONTROLLED RELEASE METFORMIN COMPOSITIONS, the specification of which

___ is attached hereto
X was filed on November 3, 2000 as Application Serial No. 09/705,630 and was amended on _____ (if applicable).
___ I hereby authorize and request our attorney, Davidson, Davidson & Kappel, LLC. of 485 Seventh Avenue, 14th Floor, New York, New York 10018 to insert here in parentheses (Application number _____, filed _____) the filing date and application number of said application when known.

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 all information which is known to me to be material to the patentability of this application as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and/or provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign and/or provisional application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR APPLICATION(S)			Priority claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint Clifford M. Davidson, Registration No. 32,728, Leslye B. Davidson, Registration No. 38,854, Cary S. Kappel, Registration No. 36,561, William C. Gehris, Registration No. 38,156, Morey B. Wildes, Registration No. 36,968, Robert J. Paradiso, Registration No. 41,240, Erik R. Swanson, Registration No. 40,833, Scott L. Appelbaum, Registration No. 41,587, Cynthia R. Moore, Registration No. 46,086, David Knasiak, Registration No. 45,991, Salvatore J. Maiorino, Registration No. 42,830, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; correspondence address: DAVIDSON, DAVIDSON & KAPPEL, LLC, 485 Seventh Avenue, 14th Floor, New York, New York 10018; Telephone: (212) 736-1940; Fax: (212) 736-2427.

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 Chih-Ming Chen

Inventor's signature [signature]

Date 3/14/01

Residence (city) _____, (state or country) _____

Citizenship UNITED STATES

Post Office Address: _____

Full name of joint Inventor, if any Xiu-Xiu Cheng

Second Inventor's signature [signature]

Date 3/27/01

Residence (city) _____, (state or country) _____

Citizenship UNITED STATES

Post Office Address: _____

Full name of joint Inventor, if any Steve Jon

Third Inventor's signature

Date 3/28/01

Residence (city) , (state or country)

Citizenship UNITED STATES

Post Office Address:

Full name of joint Inventor, if any Joseph Chou

Fourth Inventor's signature Joseph Chou

Date 3/1/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
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09-09-1998

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Conveying Party(ies)

[ ] Mark if additional names of conveying parties attached

Name (line 1): Chih-Ming Chen — Execution Date Month Day Year: 08 25 98

Name (line 2):

Second Party
Name (line 1): Xiu Xiu Cheng — Execution Date Month Day Year: 08 26 98

Name (line 2):

Receiving Party

[ ] Mark if additional names of receiving parties attached

Name (line 1): ANDRX PHARMACEUTICALS, INC.

Name (line 2): A Florida Corporation

Address (line 1): 4001 S.W. 47th Avenue

Address (line 2): Suite 201

Address (line 3): Fort Lauderdale (City) FL (State/Country) 33314 (Zip Code)

[ ] If document to be recorded is an assignment and the receiving party is not domiciled in the United States, an appointment of a domestic representative is attached. *(Designation must be a separate document from Assignment.)*

Domestic Representative Name and Address

Enter for the first Receiving Party only.

Name:

Address (line 1):

Address (line 2):

Address (line 3):

Address (line 4):

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ARBINDO EX. 1017, 76

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Expires 06/30/99
OMB 0651-0027

U.S. Department of Commerce
Patent and Trademark Office
PATENT

Correspondent Name and Address

Area Code and Telephone Number (212) 302-8989

Name: Martin P. Endres, Esq.

Address (line 1): HEDMAN, GIBSON & COSTIGAN, P.C.

Address (line 2): 1185 Avenue of the Americas

Address (line 3): New York, NY 10036

Address (line 4):

Pages

Enter the total number of pages of the attached conveyance document including any attachments. # 1

Application Number(s) or Patent Number(s)

☐ Mark if additional numbers attached

Enter either the Patent Application Number or the Patent Number (DO NOT ENTER BOTH numbers for the same property).

Patent Application Number(s)			Patent Number(s)		

If this document is being filed together with a new Patent Application, enter the date the patent application was signed by the first named executing inventor.

Month 08 Day 25 Year 98

Patent Cooperation Treaty (PCT)

Enter PCT application number only if a U.S. Application Number has not been assigned.

PCT ____ PCT ____ PCT ____

PCT ____ PCT ____ PCT ____

Number of Properties

Enter the total number of properties involved. # 1

Fee Amount

Fee Amount for Properties Listed (37 CFR 3.41): $ 40.00

Method of Payment: Enclosed [x] Deposit Account [ ]

Deposit Account

(Enter for payment by deposit account or if additional fees can be charged to the account.)

Deposit Account Number: # 08-1540

Authorization to charge additional fees: Yes [xx] No [ ]

Statement and Signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. Charges to deposit account are authorized, as indicated herein.

Martin P. Endres, Esq. — Name of Person Signing

Signature

8/31/98 — Date

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jc588 U.S. PTO
09/143776
08/31/98

Conveying Party(ies)

☐ Mark if additional names of conveying parties attached

Enter additional Conveying Parties

Name (line 1): Joseph Chou — Execution Date (Month Day Year): 08 26 98

Name (line 2):

Name (line 1): Steve Jan — Execution Date (Month Day Year): 08 26 98

Name (line 2):

Name (line 1): — Execution Date (Month Day Year):

Name (line 2):

Receiving Party(ies)

☐ Mark if additional names of receiving parties attached

Enter additional Receiving Party(ies)

Name (line 1):

Name (line 2):

Address (line 1):

Address (line 2):

Address (line 3): City / State/Country / Zip Code

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Name (line 2):

Address (line 1):

Address (line 2):

Address (line 3): City / State/Country / Zip Code

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Application Number(s) or Patent Number(s)

☐ Mark if additional numbers attached

Enter either the Patent Application Number or the Patent Number (DO NOT ENTER BOTH numbers for the same property).

Patent Application Number(s)			Patent Number(s)		

Docket No.: 141-153

ASSIGNMENT

In consideration of One Dollar and other good and valuable consideration, of which we acknowledge receipt, Chih-Ming Chen, Xiu Xiu Cheng, Joseph Chou, and Steve Jan, respectively, sell and assign to Andrx Pharmaceuticals, Inc. of 4001 S.W. 47th Avenue, Suite 201, Fort Lauderdale, FL 33314, a Florida Corporation, its successors and assigns, the entire right, title and interest in and to the improvements in and to our invention for CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE invented by us, as described in the application for United States patent filed concurrently herewith, and all applications for patent and patents therefor in any and all countries, including all thereof, and all rights of priority resulting from the filing of said United States application, and authorize and request any official whose duty it is to issue patents, to issue any patent on said improvements or resulting therefrom to said Andrx Pharmaceuticals, Inc. and agree that on request and without further consideration, but at the expense of Andrx Pharmaceuticals, Inc., we will communicate to Andrx Pharmaceuticals, Inc. any facts known to us respecting said improvements and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid Andrx Pharmaceuticals, Inc. to obtain and enforce proper patent protection for said improvements in all countries.

8/25, 1998 — Chih-Ming Chen

8/26, 1998 — Xiu Xiu Cheng

8/26, 1998 — Joseph Chou

8/26, 1998 — Steve Jan

OIPE IAP20
JUL 12 2007
PATENT & TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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JUNE 20, 2001

PTAS

101680596A

DAVIDSON, DAVIDSON & KAPPEL, LLC
ROBERT J. PARADISO
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NEW YORK 10018

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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

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NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CHEN, CHIH-MING

DOC DATE: 03/14/2001

ASSIGNOR:
CHENG, XIU-XIU

DOC DATE: 03/22/2001

ASSIGNOR:
JAN, STEVE

DOC DATE: 03/28/2001

ASSIGNOR:
CHOU, JOSEPH

DOC DATE: 03/01/2001

ASSIGNEE:
ANDRX CORPORATION
4001 SW 47TH AVENUE
FORT LAUDERDALE, FLORIDA 33314

SERIAL NUMBER: 09705630
PATENT NUMBER:

FILING DATE: 11/03/2000
ISSUE DATE:

RECEIVED
JUN 27 2001
DAVIDSON, DAVIDSON & KAPPEL

ALLYSON PURNELL, EXAMINER
ASSIGNMENT DIVISION
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To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party: **Chih-Ming Chen, Xiu-Xiu Cheng, Steve Jan, and, Joseph Chou**

Additional name(s) of conveying party(ies) attached?
[ ] Yes [X] No

2. Name and address of receiving party:

Name: **Andrx Corporation**

Internal Address: _____

Street Address: **4001 SW 47th Avenue**

City: **Fort Lauderdale** State: **Florida** ZIP: **33314**
Country: **United States**

Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of conveyance:
[X] Assignment [ ] Merger
[ ] Security Agreement [ ] Change of Name
[ ] Other _____

Execution Date(s): **3/14/01; 3/22/01; 3/28/01; and, 3/1/01, respectively**

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No. **09/705,630**
Filed on **November 3, 2000**

B. Patent No.(s)

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **Davidson, Davidson & Kappel, LLC**

Internal Address: _____

Street Address: **485 Seventh Avenue 14th Floor**

City: **New York** State: **New York** ZIP: **10018**

6. Total number of applications and patents involved: [1]

7. Total fee (37 CFR 3.41).....$ **40.00**
[X] Enclosed
[] Authorized to be charged to deposit account

8. Deposit account number: **50-0552**

04/17/2001 DBYRNE 00000162 09705630
01 FC:581 40.00 OP

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Robert J. Paradiso
Name of Person Signing

Signature

April 2, 2001
Date

Total number of pages including cover sheet, attachments, and document: [3]

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

Docket No.:**300.1005**

ASSIGNMENT

WHEREAS, We, **Chih-Ming Chen, Xiu-Xiu Cheng, Steve Jan,** and **Joseph Chou,** residing at 10680 SW 40th Manor, Davie, Florida 33328, United States; 3150 W. Rolling Hills Circle #506, Davie, Florida 33328, United States; 512 NW 120 Drive, Coral Springs, Florida 33071, United States; 6232 Traywood Lane, Manassas, Virginia 20112, United States;
respectively, (ASSIGNORS), have invented certain new and useful improvements in **CONTROLLED RELEASE METFORMIN COMPOSITIONS**, an application for a Patent of the United States for which:

__ We are about to execute;
__ was executed on_____ (date(s));
X is identified by Davidson, Davidson & Kappel, LLC, Docket No. **300.1005**;
X was filed on **November 3, 2000** Serial No. **09/705,630**.
__ we hereby authorize and request our attorney, Davidson, Davidson & Kappel, LLC of 485 Seventh Avenue, 14th Floor, New York, New York 10018 to insert here in parentheses (Application number _____, filed _____) the filing date and application number of said application when known.

and WHEREAS, **Andrx Corporation**, of **Fort Lauderdale, Florida 33314**, ASSIGNEE, is desirous of obtaining the entire right, title and interest in, to and under the said invention and the said application:

NOW, THEREFORE, In consideration of the sum of One Dollar ($1.00) to us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said ASSIGNORS, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, the entire right, title and interest in, to and under the said invention, and the said United States application and all divisions, renewals and continuations thereof, and all Patents of the United States which may be granted thereon and all reissues and extensions thereof; and all applications for industrial property protection, including, without limitation, all applications for patents, utility models, and designs which may hereafter be filed for said invention in any country or countries foreign to the United States, together with the right to file such applications and the right to claim for the same the priority rights derived from said United States application under the Patent Laws of the United States, the International Convention for the Protection of Industrial Property, or any other international agreement or the domestic laws of the country in which any such application is filed, as may be applicable; and all forms of industrial property protection, including, without limitation, patents, utility models, inventors' certificates and designs which may be granted for said invention in any country or countries foreign to the United States and all extensions, renewals and reissues thereof;

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AND WE HEREBY authorize and request the Commissioner of Patents and Trademarks of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents or other evidence or forms of industrial property protection on applications as aforesaid, to issue the same to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant and agree that we have full right to convey the entire interest herein assigned, and that we have not executed, and will not execute, any agreement in conflict herewith.

AND WE HEREBY further covenant and agree that we will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to us respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing, reissue and foreign applications, make all rightful oaths, and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper protection for said invention in all countries.

IN TESTIMONY WHEREOF, we hereunto set our hand and seal the day and year set opposite our signatures.

Dated: 3/14/01, 2001

(Signature of Inventor)

Chih-Ming Chen
(Typed Name of Inventor)

Dated: 3/22/01, 2001

(Signature of Inventor)

Xiu-Xiu Cheng
(Typed Name of Inventor)

Dated: 3/28/01, 2001

(Signature of Inventor)

Steve Jan
(Typed Name of Inventor)

Dated: 3/1/01, 2001

(Signature of Inventor)

Joseph Chou
(Typed Name of Inventor)

AUROBINDO EX. 1017, 84

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chen et al.
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	141-596 B

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☑ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Martin P. Endres		
Date	July 9, 2007	Reg. No.	35,498

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or 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 on the date shown below:

Signature			
Typed or printed name	Martin P. Endres	Date	July 9, 2007

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 2 hours 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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OIPE IAP20 JUL 12 2007 PATENT & TRADEMARK OFFICE

PTO/SB/22 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2006** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 141-596 B
Application Number 11/225,741	Filed September 13, 2005
For Controlled Release Metformin Compositions	
Art Unit 1618	Examiner Micah Paul Young

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

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

		Fee	Small Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$120	$60	$ 120.00
☐	Two months (37 CFR 1.17(a)(2))	$450	$225	$
☐	Three months (37 CFR 1.17(a)(3))	$1020	$510	$
☐	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
☐	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

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

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

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

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

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-1540. I have enclosed a duplicate copy of this sheet.

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

I am the

☐ applicant/inventor.

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

☑ attorney or agent of record. Registration Number 35,498

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

Signature	July 9, 2007 Date
Martin P. Endres Typed or printed name	212-302-8989 Telephone Number

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

☑ Total of 1 forms are submitted.

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

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

07/12/2007 SFELEKE1 00000028 11225741 120.00 OP
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UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/225,741	09/13/2005	Chih-Ming Chen	300.1005CON	3874

23280 7590 03/07/2007

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

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

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

AUROBINDO EX. 1017, 87

Office Action Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

-- 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 *08 January 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) *43-81* 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) *43-81* 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/8/07 has been entered.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 43-76 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46,52-54 of copending Application No. 11/224,785. The claims of the instant invention are drawn to a controlled release oral dosage form comprising from 1000 to 2000 mg of metformin and a carrier. The claims recite specific mean maximum plasma concentration (Cmax) values are identical to the '785 claims. The

difference between the instant claims and those of the '785 invention is that the '785 claims are silent to the particular in-vitro testing apparatus used, however these testing apparatuses are standard in the art and do not impart a particular patentable distinction on the actual; compound or formulation being tested. Since the results of the tests (Cmax) are identical for each set of claims although the instinct claims recite the particular test, it is the position of the Examiner that claims are not patentably distinct and would serve as art over one another. A further difference is that the '785 claims recite a membrane surrounding a tablet core while the instant claims are silent to a particular form. However the claims of the instant invention are open to a controlled release layer/membrane and mention a core and membrane in latter independent claims. Again it is the position of the Examiner that the claims would act as opposing art over one another if issues and therefor are not patentably distinct.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

3. 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 –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 43-81 are rejected under 35 U.S.C. 102(a,e) as being anticipated by Chen et al (USPN 6,099,862 hereafter '862). The claims are drawn to a controlled release formulation comprising metformin a carrier material in a matrix. The formulation comprises a membrane coating and a passageway through said coating, where the controlled releasing carrier includes cellulose derivatives.

5. The '862 patent teaches a controlled release formulation comprising a core and a surrounding membrane with a passageways thought he membrane (col. 2, lin. 38-57). The drug in the core is metformin while the absorption enhancers include PEG 400, plasticizers including citric acid and triacetin (col. 4, lin. 20-50, examples). The core comprises carries such as hydroxypropylcellulose and other water-soluble cellulose derivatives (col. 3, lin. 21-30). The membrane polymer comprises various celluloses such as cellulose ethers (col. 3, lin. 65-col. 4, lin. 4). The formulation has an in vitro dissolution profile where approximately 23% of the metformin in the core is dissolved within the first 2 hours of release (example 2). This is verified in simulated intestinal fluid on an Apparatus Type II paddle method according to the United States Pharmacopoeia procedures operating at 75 rpm (example 2).

6. Regarding the Cmax values recited in the claims, it is the position of the Examiner that such limitations do not impart patentability on the claims. These limitations are seen as future intended uses for known formulations. Further, the claims recite that they are based on varying concentrations of the metformin, meaning the Cmax values are hypothetical at best. It is the

position of the Examiner that any formulation matching the physical components as that of the instant claims, namely a metformin compound in a matrix with a controlled release carrier would be capable of achieving these Cmax values, and would inherently achieve these values. Also the claim recite that the formulation only be suitable for once-a-day administration, which is again a future intended use for the formulation. Any formulation can be made suitable for any type of administration. It is the position of the Examiner that such a limitation does not impart patentability.

7. Specifically regarding the Cmax values that are dependent on a specific hypothetical release concentration, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

8. For these reasons it is the position of the Examiner the '862 patent anticipates the instant claims.

Response to Arguments

9. Applicant's arguments with respect to claims 43-81 have been considered but are moot in view of the new ground(s) of rejection.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Micah-Paul Young whose telephone number is 571-272-0608. The examiner can normally be reached on M-F 7:00-4:30 every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. 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.

Micah-Paul Young
Examiner
Art Unit 1618

MP Young

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Notice of References Cited	Application/Control No. 11/225,741	Applicant(s)/Patent Under Reexamination CHEN ET AL.	
	Examiner Micah-Paul Young	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,099,862	08-2000	Chen et al.	424/473
	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
11/225,741	CHEN ET AL.
Examiner	**Art Unit**
Micah-Paul Young	1618

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/225,741	CHEN ET AL.	
Examiner	**Art Unit**	
Micah-Paul Young	1618	

SEARCHED			
Class	Subclass	Date	Examiner
424	464, 469, 450,484	12/8/2005	MPY
514	414,415		
above	to date	6/17/2006	
above	to date	2/27/2007	

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
east brs search (all databases searched) odp with 11/224,784	12/8/2008	MPY
search updated 6/21/06		
search updated 2/27/07		

OIPE IAP95 JAN 08 2007 PATENT & TRADEMARK OFFICE

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Serial No.:	11/225,741
	Application of:	Chih-Ming Chen, et al.
	Filed:	September 13, 2005
	For:	**Controlled Release Metformin Compositions**
	Examiner:	Young, Micah Paul
	Art Unit:	1618
	Docket No.:	300.1005CON2
	Customer No.:	23280

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

January 3, 2007

AMENDMENT

Sir:

In response to the Final Office Action of July 3, 2006, Applicants submit the following:

Amendments to the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

I. AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of the Claims

Claims 1-42 (Cancelled)

Claim 43. (Currently Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 44. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 45. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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Claim 46. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 47. (Currently Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 48. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 49. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 50. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 51. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

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Claim 52. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 53. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 54. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 55. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 56. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 57. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 58. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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Claim 59. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 60. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 61. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 62. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 63. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 64. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 65. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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Claim 66. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 67. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 68. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 69. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 70. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 71. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 72. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 8600 ng/ml to about 16950 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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Claim 73. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 12900 ng/ml to about 25425 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 74. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 21500 ng/ml to about 42375 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 75. (Previously presented) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

Claim 76. (Currently Amended) The controlled release oral dosage form of claim 43, comprising a core comprising said metformin or pharmaceutically acceptable salt thereof and a membrane surrounding said core said membrane comprising the controlled release carrier ~~a hydrophobic material~~.

Claim 77. (Previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises a binding agent.

Claim 78. (Previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises an absorption enhancer.

Claim 79. (Previously presented) The controlled release oral dosage form of claim 76, further comprising a passageway in the membrane.

Claim 80. (Currently Amended) The controlled release oral dosage form of claim 76, wherein said controlled release carrier ~~membrane~~ comprises a polymer selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether,

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cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate

Claim 81. (Previously presented) The controlled release oral dosage form of claim 80, wherein said membrane further comprises a plasticizer.

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II. REMARKS

A. Status of the Claims

Claims 43-81 are currently pending. Claims 43, 47, 76 and 80 have been amended without prejudice. Support for these amendments can be found throughout the specification as originally filed, e.g. at page 20, lines 1-2 and the examples. It is respectfully submitted that no new matter has been added by virtue of the present amendment.

B. Double Patenting

In the Office Action, the Examiner provisionally rejected claims 43-76 "on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46 and 52-54 of co-pending Application No. 11/224,785."

In response, as the obviousness type double patenting rejection is provisional, Applicants respectfully submit that the filing of a terminal disclaimer to obviate the double-patenting rejection will be considered upon indication that the claims are otherwise allowable.

C. Rejection Under 35 U.S.C. § 102

In the Office Action, claims 43-45, 47-49, 51-53, 55-57, 59-61, 63-65, 67-69, 71-73 and 75 were rejected under 35 U.S.C. § 102 (a and e) as being anticipated by U.S. Patent No. 6,011,049 to Whitcomb. The Office Action stated that "it is the position of the Examiner that the formulations of the '049 would inherently possess [the recited] properties since ... applicant has not provided any other defining features of the claims."

Although Applicants disagree with this rejection, the claims have been amended to recite further "defining features" over the '049 reference. By virtue of the present amendment, the present claims have been amended to recite that the controlled release carrier "is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating".

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Applicants respectfully submit that the '049 reference does not teach or suggest formulations comprising metformin and a controlled release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating as recited in the present claims. Applicants submit that Whitcomb only incidentally mentions a controlled release formulation at column 4, lines 35-38 and a slow release form at column 5, lines 30-34. Whitcomb fails to teach how such formulations are made, whether such formulations are suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof, and whether such formulations provide a mean Cmax as recited in claims 43 and 47. Therefore, as the present claims recite further "defining features" which are not taught or suggested by the '049 reference, the Examiner's position that the Whitcomb formulations inherently posses the presently claimed in-vitro and in-vivo parameters is now moot.

Regardless of the further defining features in the claims, Applicants respectfully submit that the claimed pharmacokinetic parameters are not inherent in the formulations of Whitcomb. The Examiner is reminded that to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

It is respectfully submitted that the Examiner has not met his burden of proof to make an inherency rejection as there is no indication in Whitcomb that the claimed Cmax of the present invention must be "necessarily present" in the formulations described in Whitcomb. Whitcomb fails to teach how such controlled release formulations are made, and there is no indication in the Examples that Whitcomb even contemplates the use of metformin or a pharmaceutically

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acceptable salt there in a controlled release dosage form with the pharmacokinetic parameters recited in the present claims.

As the Whitcomb reference does not provide any guidance for preparing a controlled release metformin formulation, Applicants respectfully submit that it is only through the impermissible use of hindsight reasoning that the Examiner is rejecting the present pharmacokinetic parameters as inherent in the Whitcomb formulations. See MPEP, 8th Edition, section 2141 ("[t]he reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention").

In fact, the only particular guidance with respect to metformin formulations suitable for the purported invention of the '049 patent is at column 4, lines 60-61, which states that metformin "is available in tablets which contain 500 mg and 850 mg of active agent. These can be given up to two times a day or more." Applicants submit that one skilled in the art would recognize that the inventors of the '049 patent are referring to the commercial product Glucophage® as being suitable for use in their purported invention. Applicants submit that Glucophage® is an immediate release formulation, as opposed to the controlled release formulations of the present invention.

The Examiner is further directed to the Examples of Whitcomb which indicate that in the study with metformin and troglitazone, 1000 mg metformin is administered in the study "BID" (twice a day), while 400 mg troglitazone is administered "QD" (once a day). See, e.g., col. 14, lines 21-24 of Whitcomb.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to formulate a controlled release oral dosage form suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof as recited in the present claims, in view of Whitcomb's description of the administration of metformin hydrochloride to

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be given up to two times a day or more, and Whitcomb's exemplification of the administration of 1000 mg on a twice a day basis.

Applicants further submit that even if the general description of a controlled release formulation in the Whitcomb reference could be manipulated by one skilled in the art to arrive at the present invention, such action would be the result of optimization of conditions, which is not a proper basis for inherency. See *In re Rijckaert*.

In view of the arguments presented above, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (a and e) over the '049 reference be removed.

D. Rejection Under 35 U.S.C. § 103

1. Claim rejections over Whitcomb

In the Office Action, claims 43-75 were rejected under 35 U.S.C. § 103 (a) as being obvious over U.S. Patent No. 6,011,049 to Whitcomb. The Office Action referred to the earlier § 102 (a and e) rejection, and stated that "it is further the position of the Examiner that the Cmax values would be inherent ... since the products of the art and the instant claims appear identical yet the disclosure are silent to the pharmacokinetics."

In response, Applicants respectfully submit that as discussed above, the claims have been amended to recite formulations "comprising (a) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof and (b) a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating." These are further limitations to establish that the products of the art and the instant claims are not "identical".

Therefore, as the present claims recite further limitations to establish that the formulations of the prior art and the present claims are not identical, the Examiner's position that the formulations of Whitcomb inherently posses the presently claimed in-vitro and in-vivo parameters is now moot.

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Further, Applicants again submit that regardless of defining features in the claims, the claimed pharmacokinetic parameters are not inherent in the formulations of Whitcomb in view of the positions presented above with respect to the § 102 (a and e) rejections.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 (a) over Whitcomb be removed.

2. Claims rejections over Whitcomb in view of Chen

In the Office Action, claims 43 and 76-81 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of Whitcomb and Chen et al. (U.S. Patent No. 6,099,862).

This rejection is traversed. Applicants respectfully submit that one skilled in the art would not be motivated to combine Whitcomb and Chen et al. as each reference is directed to different combinations of dual drug therapy.

Applicants respectfully submit that even if these references were combined, one skilled in the art would not be motivated to prepare the presently claimed composition, which has been amended to recite that the active agent consists of metformin or a pharmaceutically acceptable salt. Chen et al. is directed to a composition which includes two active agents, namely, an antihyperglycemic drug (e.g., metformin) and a hypoglycemic drug (e.g., a sulfonylurea). The Examiner is reminded that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." (Emphasis included) *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F. 2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Accordingly, Applicants submit that, upon viewing the references as a whole, the combination of the Chen reference with the Whitcomb reference would result in a formulation which must include both an antihyperglycemic drug and a hypoglycemic drug, which is excluded by the present claims by virtue of the closed ended "consisting of" transitional phrase.

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Applicants further submit that Chen et al. does not teach or suggest the presently claimed Cmax limitation and therefore does not cure this deficiency of Whitcomb.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the combined disclosures of Whitcomb and Chen et al. be removed.

E. Conclusion

It is respectfully submitted that in view of the actions taken an arguments presented, that this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
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PTO/SB/30 (04-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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RCE/IFW

Request For Continued Examination (RCE) Transmittal

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

Application Number	11/225,741
Filing Date	September 13, 2005
First Named Inventor	Chih-Ming CHEN
Art Unit	1618
Examiner Name	Paul Micah YOUNG
Attorney Docket Number	300.1005CON2

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
ii. ☐ Other _____

b. ☒ Enclosed

i. ☒ Amendment/Reply
ii ☐ Affidavit(s)/Declaration(s)
iii. ☐ Information Disclosure Statement (IDS)
iv. ☒ Other Petition For Extension of Time

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 50-0552 . I have enclosed a duplicate copy of this sheet.

i. ☒ RCE fee required under 37 C.F.R. 1.17(e)
ii. ☒ Extension of time fee (37 C.F.R. 1.136 and 1.17)
iii. ☐ Other _____

b. ☒ Check in the amount of $ 1690.00 enclosed

c. ☐ Payment by credit card (Form PTO-2038 enclosed)

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature		Date	January 3, 2007
Name (Print /Type)	Robert J. Paradiso	Registration No. (Attorney/Agent)	41,240

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: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print /Type)	Oleg Iosselevich	Date	January 3, 2007

This collection of information is required by 37 CFR 1.114. 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 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: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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OIPE IAP96 JAN 0 8 2007 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Chih-Ming CHEN, et al.
Serial No.:	11/225,741
Filed:	September 13, 2005
For:	**CONTROLLED RELEASE METFORMIN COMPOSITIONS**
Examiner:	YOUNG, Micah Paul
Group Art Unit:	1618

Mail Stop: RCE
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

January 3, 2007

PETITION FOR EXTENSION UNDER 37 CFR § 1.136(a)(1)

S I R:

Applicants petition the Commissioner for Patents to extend the time for filing an Amendment in the above matter, for three months from October 3, 2006 to January 3, 2007.

A check in the amount of $1690.00 is enclosed, $900.00 of which covers the (3) months extension fee. Applicants note that the fee for a (1) month extension of time in the amount of $120.00 was previously submitted with Applicant's October 19, 2006 Response. If it is determined that any additional fees are due or if any fees have been overpaid, the Commissioner is hereby authorized to charge the deficiency or credit the overpayment to Deposit Account No. 50-0552.

01/09/2007 MWOLDGE1 00000047 11225741
02 FC:1253 900.00 OP

Respectfully submitted,
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PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/225,741	09/13/2005	

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 01/08/2007	(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))	* 39	Minus	** 39	= 0	X $ =		OR	X $50=	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 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:
Juliet McMillan

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/225,741	09/13/2005	Chih-Ming Chen	300.1005CON	3874

23280 7590 11/13/2006

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NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 11/13/2006

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

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

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

THE REPLY FILED 23 October 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *43-81*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. NOTE: The claim amendments recite a tablet matrix which was never claimed in previous prosecutions. These newly recited limitations require further consideration.

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/225,741	CHEN ET AL.	
Examiner	**Art Unit**	
Micah-Paul Young	1618	

SEARCHED			
Class	Subclass	Date	Examiner
424	464, 489, 450, 484	12/8/2005	MPY
514	414, 415		
above	to date	6/17/2005	MPY
above	to date	11/1/2006	MPY

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
east brs search updated odp with 11/224784	12/8/2005	MPY
search updated 6/21/06		
search updated 11/1/06		

OIPE
OCT 2 3 2006
IAP51
PATENT & TRADEMARK OFFICE

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Serial No.:	11/225,741
	Application of:	Chih-Ming Chen, et al.
	Filed:	September 13, 2005
	For:	**Controlled Release Metformin Compositions**
	Examiner:	Young, Micah Paul
	Art Unit:	1618
	Docket No.:	300.1005CON2
	Customer No.:	23280

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

October 19, 2006

AMENDMENT

Sir:

In response to the Final Office Action of July 3, 2006, Applicants submit the following:

Amendments to the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

I. AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of the Claims

Claims 1-42 (Cancelled)

Claim 43. (Currently Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 44. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 45. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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Claim 46. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 47. (Currently Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 48. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 49. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 50. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 51. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

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Claim 52. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 53. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 54. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 55. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 56. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 57. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 58. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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Claim 59. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 60. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 61. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 62. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 63. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 64. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 65. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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Claim 66. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 67. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 68. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 69. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 70. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 71. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 72. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 8600 ng/ml to about 16950 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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Claim 73. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 12900 ng/ml to about 25425 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 74. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 21500 ng/ml to about 42375 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 75. (Previously presented) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

Claim 76. (Previously presented) The controlled release oral dosage form of claim 43, comprising a core comprising said metformin or pharmaceutically acceptable salt thereof and a membrane surrounding said core said membrane comprising a hydrophobic material.

Claim 77. (Previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises a binding agent.

Claim 78. (Previously presented) The controlled release oral dosage form of claim 76, wherein said core further comprises an absorption enhancer.

Claim 79. (Previously presented) The controlled release oral dosage form of claim 76, further comprising a passageway in the membrane.

Claim 80. (Previously presented) The controlled release oral dosage form of claim 76, wherein said membrane comprises a polymer selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate

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Claim 81. (Previously presented) The controlled release oral dosage form of claim 80, wherein said membrane further comprises a plasticizer.

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II. REMARKS

A. Status of the Claims

Claims 43-81 are currently pending. Claims 43 and 47 have been amended without prejudice. Support for this amendment can be found throughout the specification as originally filed, e.g. at page 20, lines 1-2. It is respectfully submitted that no new matter has been added by virtue of the present amendment.

B. Double Patenting

In the Office Action, the Examiner provisionally rejected claims 43-76 "on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46 and 52-54 of co-pending Application No. 11/224,785."

In response, as the obviousness type double patenting rejection is provisional, Applicants respectfully submit that the filing of a terminal disclaimer to obviate the double-patenting rejection will be considered upon indication that the claims are otherwise allowable.

C. Rejection Under 35 U.S.C. § 102

In the Office Action, claims 43-45, 47-49, 51-53, 55-57, 59-61, 63-65, 67-69, 71-73 and 75 were rejected under 35 U.S.C. § 102 (a and e) as being anticipated by U.S. Patent No. 6,011,049 to Whitcomb. The Office Action stated that "it is the position of the Examiner that the formulations of the '049 would inherently possess [the recited] properties since ... applicant has not provided any other defining features of the claims."

Although Applicants disagree with this rejection, the claims have been amended to recite further "defining features" over the '049 reference. By virtue of the present amendment, the present claims have been amended to recite that the controlled release carrier "is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating".

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Applicants respectfully submit that the '049 reference does not teach or suggest formulations comprising metformin and a controlled release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating as recited in the present claims. Therefore, as the present claims recite further "defining features" which are not taught or suggested by the '049 reference, the Examiner's position that the Whitcomb formulations inherently posses the presently claimed in-vitro and in-vivo parameters is now moot.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (a and e) over the '049 reference be removed.

D. Rejection Under 35 U.S.C. § 103

1. Claim rejections over Whitcomb

In the Office Action, claims 43-45, 47-49, 51-53, 55-57, 59-61, 63-65, 67-69, 71-73 and 75 were rejected under 35 U.S.C. § 103 (a) as being obvious over U.S. Patent No. 6,011,049 to Whitcomb. The Office Action referred to the earlier § 102 (a and e) rejection, and stated that "it is further the position of the Examiner that the Cmax values would be inherent ... since the products of the art and the instant claims appear identical yet the disclosure are silent to the pharmacokinetics."

In response, Applicants respectfully submit that, as discussed above, the claims have been amended to recite formulations "comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating". These are further limitations to establish that the products of the art and the instant claims are not "identical".

Therefore, as the present claims recite further limitations to establish that the formulations of the prior art and the present claims are not identical, the Examiner's position that the formulations of the '049 reference inherently posses the presently claimed in-vitro and in-vivo parameters is now moot.

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Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 (a) over the '049 reference be removed.

2. Claims rejections over Whitcomb in view of Chen

In the Office Action, claims 43 and 76-81 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of Whitcomb and Chen et al. (U.S. Patent No. 6,099,862).

This rejection is traversed. Applicants respectfully submit that one skilled in the art would not be motivated to combine the '049 reference and the '862 reference as each reference is directed to different combinations of dual drug therapy.

However, even assuming that the references are properly combinable, one skilled in the art would not arrive at the presently claimed invention. As discussed above, the '049 reference does not teach or suggest a formulation comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier which is incorporated into a matrix along with the metformin, or which is applied as a controlled release coating, wherein the formulation exhibits the claimed in-vitro and in-vitro parameters. The '862 reference does not cure the deficiencies of the '049 reference, as it does not teach or suggest the claimed Tmax limitation.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the combined disclosures of the '862 reference and the '049 reference be removed.

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E. Conclusion

It is respectfully submitted that in view of the actions taken an arguments presented, that this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

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AUROBINDO EX. 1017, 129

OIPE
OCT 23 2006
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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Chih-Ming CHEN, et al.
Serial No.:	11/225,741
Filed:	September 13, 2005
For:	**CONTROLLED RELEASE METFORMIN COMPOSITIONS**
Examiner:	YOUNG, Micah Paul
Group Art Unit:	1618

Mail Stop: AF
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

October 19, 2006

PETITION FOR EXTENSION UNDER 37 CFR § 1.136(a)(1)

S I R:

Applicants petition the Commissioner for Patents to extend the time for filing an Amendment in the above matter, for one month from October 3, 2006 to November 3, 2006.

A check for $120.00 is enclosed, of which covers the one (1) months extension fee. If it is determined that any additional fees are due or if any fees have been overpaid, the Commissioner is hereby authorized to charge the deficiency or credit such overpayment to Deposit Account No. 50-0552.

10/24/2006 AWONDAF1 00000015 11225741
01 FC:1251 120.00 OP

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

Robert J. Paradiso
Reg. No. 41,240

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
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(212) 736-1940, Ext. 104

FORM PTO -1083
Mail Stop: AF
COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Docket No.: 300.1005CON2
Date: October 19, 2006

In re application of: Chih-Ming CHEN, et al.
Serial No.: 11/225,741
Filed: September 13, 2005
For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

S I r:

Transmitted herewith is an **Amendment** (12 pages) in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1) REMAINING AFTER AMENDMENT	(Col. 2) HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	LARGE ENTITY RATE	LARGE ENTITY FEE
FOR:								
TOTAL CLAIMS	39	Minus 34 =	5	x $	$		x $ 50	$ 250.00
INDEP. CLAIMS		Minus =	0	x $	$		x $ 200	$ 00.00
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $	$		+ $ 360	$ 00.00

TOTAL: $ OR TOTAL: $250.00

[X] Also transmitted herewith are:
[X] Petition for one month extension under 37 C.F.R. 1.136
[ ] Other:-

[X] Check(s) in the amount of **$120.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for one month extension under 37 C.F.R. 1.136
[ ] Other:

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.
[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with sufficient postage to the United States Postal Service as "first class mail" in an envelope addressed to Mail Stop: AF "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450". on November 19, 2006
DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: _____
Akil Chevalier

11/805,741

PTO/SB/06 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number

CLAIMS 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))				$____	OR		$____
TOTAL CLAIMS (37 CFR 1.16(c))	minus 20 =	*	X $____ =		OR	X $____ =	
INDEPENDENT CLAIMS (37 CFR 1.16(b))	minus 3 =	*	X $____ =		OR	X $____ =	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d))			+ $____ =		OR	+ $____ =	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		OR	TOTAL	

CLAIMS AS AMENDED – PART II

4/20/06

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	* 39	Minus	** 34	= 5
Independent (37 CFR 1.16(b))	* 3	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $____ =	250	OR	X $____ =	
X $____ =		OR	X $____ =	
+ $____ =		OR	+ $____ =	
TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

10/23/06

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	* 39	Minus	** 39	=
Independent (37 CFR 1.16(b))	* 2	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $____ =		OR	X $____ =	
X $____ =		OR	X $____ =	
+ $____ =		OR	+ $____ =	
TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	*	Minus	**	=
Independent (37 CFR 1.16(b))	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $____ =		OR	X $____ =	
X $____ =		OR	X $____ =	
+ $____ =		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.

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

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

2

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/225,741	09/13/2005	Chih-Ming Chen	300.1005CON	3874

23280 7590 07/03/2006

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 07/03/2006

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

Office Action Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

-- 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 April 2006*.

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) *43-81* 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) *43-81* 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-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment of Papers Received: Amendment/Response dated 4/20/06

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 43-76 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46,52-54 of copending Application No. 11/224,785. The claims of the instant invention are drawn to a controlled release oral dosage form comprising from 1000 to 2000 mg of metformin and a carrier. The claims recite specific mean maximum plasma concentration (Cmax) values are identical to the '785 claims. The difference between the instant claims and those of the '785 invention is that the '785 claims are silent to the particular in-vitro testing apparatus used, however these testing apparatuses are standard in the art and do not impart a particular patentable distinction on the actual; compound or formulation being tested. Since the results of the tests (Cmax) are identical for each set of claims although the instinct claims recite the particular test, it is the position of the Examiner that

claims are not patentably distinct and would serve as art over one another. A further difference is that the '785 claims recite a membrane surrounding a tablet core while the instant claims are silent to a particular form. However the claims of the instant invention are open to a controlled release layer/membrane and mention a core and membrane in latter independent claims. Again it is the position of the Examiner that the claims would act as opposing art over one another if issues and therefor are not patentably distinct.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

3. 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 –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 43-45,47-49,51-53,55-57,59-61, 63-65, 67-69, 71-73 and 75 are rejected under 35 U.S.C. 102(a and e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049). The claims are drawn to a once-a-day controlled-release dosage form comprising metformin and a control-releasing carrier. The metformin is present in concentrations from 1000 – 2000 mg and produces various Cmax values.

5. The '049 patent teaches a once-a-day oral metformin formulation for the treatment of diabetes mellitus (abstract, col. 5, lin. 7-24). The formulation comprises control-release carriers such as starch, gelatin and methylcellulose and takes the form of tablets or capsules (col. 5, lin. 27-33). The formulations comprise from 300 – 2000 mg of metformin (claims). The disclosure is silent to the particular Cmax values however the concentrations of the metformin are identical to those of the instant claims. It is the position of the Examiner that the formulations of the '049 would inherently possess these properties since the concentrations are identical and applicant has not provided any other defining features of the claims. With these things in mind, the disclosures of the '049 patent anticipate the claims.

Claim Rejections - 35 USC § 103

6. 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.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 43-45,47-49,51-53,55-57,59-61, 63-65, 67-69, 71-73 and 75 are rejected under 35 U.S.C. 102 (a and e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049).

As discussed above the '049 patent discloses a once-a-day formulation of metformin formulation comprising from 30 – 2000 mg of metformin. It is the position of the Examiner that the Cmax values would be inherent for the formulation since the concentrations are identical to those of the instant claims. It is further the position of the Examiner that the disclosures also obviate the instant claims, since the products of the art and the instant claims appear identical yet the disclosures are silent to the pharmokinetics. The Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

9. With these things in mind it would have been obvious to one of ordinary skill in the art to follow the teachings and suggestions of the '049 reference in order to provide an improved, easier method of treating diabetes mellitus. It would have been obvious to one of ordinary skill in the art to follow these teachings and suggestions with an expected result of a method of treating diabetes mellitus with a once-a-day formulation comprising a metformin compound.

10. Claims 46,50,54,58,62,66,70,74 and are rejected under 35 U.S.C. 103(a) as being unpatentable over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049).

11. As discussed above the '049 patent discloses a once-a-day metformin formulation for treating diabetes mellitus where the metformin is in concentrations from 300-2000 mg. The claims however recite a 2500 mg dosage form. It is the position of the Examiner that these increased concentrations do not impart patentability on the claims. The patent discloses the general conditions of the claims, namely the large concentration of metformin in a once-a-day dosage form. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *See* In re Aller, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

12. Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various pharmaceutical compositions having various amounts of the active is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. *See* In re Russell, 439 F.2d 1228 169 USPQ 426 (CCPA 1971).

13. With these things in mind one of ordinary skill in the art would have been motivated to optimize the concentrations of the metformin in order to deliver and improve the method of treating diabetes mellitus. It would have been obvious to follow the disclosures of the '049 patent with an expected result of an optimized once-a-day dosage from capable of treating patients with NIDDM more effectively.

14. Claims 43 and 76-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Whitcomb (USPN 6,011,049 hereafter '049) and Chen et al (USPN 6,099,862 hereafter '862). The claims are drawn to a controlled release formulation comprising metformin and a core formulation. The formulation comprises a core with a passageway opening, plasticizer, binding agents, and absorption enhancers.

15. As discussed above the '049 discloses a controlled release formulation of metformin in various forms including tablets, capsule and osmotic pumps (col. 5, lin. 27-30). However the reference is silent to the inclusion of a passageway in the membrane or specific binding agents, plasticizers and absorption enhancers in the membrane. However these components are well known in the art as seen it the '862 patent.

16. The '862 patent discloses a controlled release formulation comprising a core and a surrounding membrane with a passageways thought he membrane (col. 2, lin. 38-57). The drug in the core is metformin while the absorption enhancers include PEG 400, plasticizers including citric acid and triacetin (col. 4, lin. 20-50, examples). The membrane polymer comprises various celluloses such as cellulose ethers (col. 3, lin. 65-col. 4, lin. 4). A skilled artisan would be motivated to include the dosages of the '049 into the tablet of the '862 since not references combine metformin with other drugs in order to treat NIDDM.

17. With these things in mind it would have been obvious to combine the dosage concentrations of the '862 patent in to the dosage from of the '049 patent in order to provide a slow release osmotic pump as suggested in the '862 patent. It would have been obvious to follow the disclosures of the '049 patent with an expected result of an optimized once-a-day dosage from capable of treating patients with NIDDM more effectively.

Response to Arguments

18. Applicant's arguments filed 4/17/06 have been fully considered but they are not persuasive. Applicant argues that:

a. Whitcomb does to disclose or teach controlled release formulation or ways of formulating such dosage forms.

b. Whitcomb does not disclose once-a-day formulations of the dosage concentration of the claims.

c. Whitcomb does not disclose or teach any of the dissolution profile recited in the claims.

19. Regarding argument a., it is the position of the Examiner that the disclosures of Whitcomb at col. 4, lin. 35-37 are sufficient to meet the limitations of a controlled release formulation comprising metformin. Controlled release tablet are disclosed as possible forms of the invention. Excipients are later discussed that are typical among controlled release dosage from s including starch, glucose and talc (col. 5, lin. 27-30). Slow release forms such as osmotic pumps are also disclosed by the reference. It is the position of the Examiner that these disclosures are sufficient to meet the limitations of the claims of a controlled release metformin formulation. The claims are generally drawn to a controlled release metformin dosage for with a specific dissolution profile that would be inherent to any dosage from comprising the same physical characteristics of the formulation. Given the broadest reasonable interpretation of the claims, any formulation of 2000 mg of metformin should have the same dissolution profile as those of the instant claims, as well as being capable of the same AUC properties of the instant

claims. Essentially any dosage with a combination of components meeting the limitations of the claims would inherently posses all dissolution and pharmokenetic properties. Due to this interpretation the claims remain anticipated and obviated by the claims. Regarding applicant's arguments that the '862 patent does not disclose any methods of manufacture, it is the position of the Examiner that such arguments are spurious at best. The claims are drawn to compositions, and not methods of manufacture. As discussed above the disclosures of common excipients, and controlled release dosage forms is seen by the Examiner as sufficient disclosures of a controlled-release dosage form. With these things in mind, the disclosures of the '862 patent sufficiently anticipate and obviate the claims.

20. Regarding argument b. it is the position of the Examiner that the "once-a-day" limitations are not to be given patentable weight in a composition claim since they denote methods of use and do not limit the physical components of the dosage from in any way. The dosage forms of the instant claims further need only be suitable for "once-a-day" delivery and need not themselves actually be "once-a-day" dosages. Any dosage taken all at once can be considered "once-a-day" even if it comprises several tablets, pellets or pills. This "once-a-day" limitation renders the composition claims to a product-by-process interpretation where the process limitations are not given patentable weight. Regarding the teachings of the '049 patent, metformin is delivered in dosages as high as 2000 mg per day and can be delivered up to twice daily, meaning they are capable (the only requirements of the claims) for single daily dosage. For these reasons at least the claims remain anticipated and obviated by the prior art.

21. Regarding argument c., as discussed above it is the position of the Examiner that a combination of the same components would inherently have the same dissolution and

pharmokenetic properties. The formulations discloses and taught by the '862 patent are used to treat the same disorder as the instant claims, and possess the same concentration of active agent. Given the broadest reasonable interpretation of the claims the prior art need only disclose a 2000 mg controlled dosage form of metformin and be capable of once-a-day delivery to anticipate the claims. The metformin formulations of the '862 are control released and have 2000 mg of metformin and its pharmaceutical salts. Therefore the formulations meet the limitations of the instant claims as inherently possess the dissolution profiles and pharmokenetic properties of the instant claims, even though the '862 reference is silent to such properties. For these reason the claims remain obviated and anticipated by the prior art.

22. Regarding the new claims, they are addressed by the addition of the newly cited art.

23. For these reason the claims remain obviated and anticipated by the Whitcomb reference.

Conclusion

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

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

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Micah-Paul Young whose telephone number is 571-272-0608. The examiner can normally be reached on M-F 7:00-4:30 every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. 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.

Micah-Paul Young
Examiner
Art Unit 1618

MP Young

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

Notice of References Cited	Application/Control No. 11/225,741	Applicant(s)/Patent Under Reexamination CHEN ET AL.	
	Examiner Micah-Paul Young	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,011,049	01-2000	Whitcomb, Randall Wayne	514/369
*	B	US-6,099,862	08-2000	Chen et al.	424/473
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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FOREIGN PATENT DOCUMENTS

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	N					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	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
11/225,741	CHEN ET AL.
Examiner	**Art Unit**
Micah-Paul Young	1618

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/225,741	CHEN ET AL.	
Examiner	**Art Unit**	
Micah-Paul Young	1618	

SEARCHED			
Class	Subclass	Date	Examiner
424	464, 469, 450, 484	12/8/2005	MPY
514	414, 415		
above	to date	6/17/2005	MPY

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
east brs search (all databases searched) odp with 11/224,784	12/8/2005	MPY
search updated 6/21/06		

11/205 741

PTO/SB/06 (08-03)
Approved for use through 7/31/2006. 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

CLAIMS 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))				$____	OR		$____
TOTAL CLAIMS (37 CFR 1.16(c))	minus 20 =	*	X $____ =		OR	X $____ =	
INDEPENDENT CLAIMS (37 CFR 1.16(b))	minus 3 =	*	X $____ =		OR	X $____ =	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d))			+ $____ =		OR	+ $____ =	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		OR	TOTAL	

CLAIMS AS AMENDED – PART II

4/20/06

AMENDMENT A

	(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(c))	* 39	Minus	** 34	= 5	X $____ =	250.00	OR	X $____ =	
Independent (37 CFR 1.16(b))	* 3	Minus	*** 3	=	X $____ =		OR	X $____ =	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))					+ $____ =		OR	+ $____ =	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
Total (37 CFR 1.16(c))	*	Minus	**	=	X $____ =		OR	X $____ =	
Independent (37 CFR 1.16(b))	*	Minus	***	=	X $____ =		OR	X $____ =	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))					+ $____ =		OR	+ $____ =	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
Total (37 CFR 1.16(c))	*	Minus	**	=	X $____ =		OR	X $____ =	
Independent (37 CFR 1.16(b))	*	Minus	***	=	X $____ =		OR	X $____ =	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))					+ $____ =		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.

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

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

2

OIPE IAP28
APR 20 2006
PATENT & TRADEMARK OFFICE

UNITED STATES PATENT & TRADEMARK OFFICE

Serial No.:	11/225,741
Application of:	Chih-Ming Chen, et al.
Filed:	September 13, 2005
For:	**Controlled Release Metformin Compositions**
Examiner:	Young, Micah Paul
Art Unit:	1618
Docket No.:	300.1005CON2
Customer No.:	23280

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

April 17, 2006

AMENDMENT

S i r:

Sir:

In response to the Office Action of December 16, 2005, Applicants submit the following:

Amendments to the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

04/20/2006 HDESTA1 00000021 11225741
02 FC:1202 250.00 OP

I. AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of the Claims

Claims 1-42 (Cancelled)

Claim 43. (Previously presented) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 44. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 45. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 46. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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Claim 47. (Previously presented) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 48. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 49. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 50. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 51. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 52. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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Claim 53. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 54. (Previously presented) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 55. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 56. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 57. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 58. (Previously presented) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 59. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

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Claim 60. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 61. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 62. (Previously presented) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 63. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 64. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 65. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 66. (Previously presented) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

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Claim 67. (Previously presented) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 68. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 69. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 70. (Previously presented) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 71. (Previously presented) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 72. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 8600 ng/ml to about 16950 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 73. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 12900 ng/ml to about 25425 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

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Claim 74. (Previously presented) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 21500 ng/ml to about 42375 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 75. (Previously presented) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

Claim 76. (Currently Amended) The controlled release oral dosage form of claim 43, ~~wherein said~~ comprising a core comprising said metformin or pharmaceutically acceptable salt thereof ~~is a tablet core~~ and ~~said~~ a membrane ~~comprise~~ surrounding said core said membrane comprising a hydrophobic material.

Claim 77. (New) The controlled release oral dosage form of claim 76, wherein said core further comprises a binding agent.

Claim 78. (New) The controlled release oral dosage form of claim 76, wherein said core further comprises an absorption enhancer.

Claim 79. (New) The controlled release oral dosage form of claim 76, further comprising a passageway in the membrane.

Claim 80. (New) The controlled release oral dosage form of claim 76, wherein said membrane comprises a polymer selected from the group consisting of cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate

Claim 81. (New) The controlled release oral dosage form of claim 80, wherein said membrane further comprises a plasticizer.

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II. REMARKS

A. Status of the Claims

Claims 43-81 are currently pending. Claim 76 has been amended without prejudice. New Claims 77-81 have been added. Support for new claim 77 can be found at page 6, lines 18-24 and at page 32, Table 5. Support for new claims 78-81 can be found at page 7, lines 4-10, at page 8, lines 6-9 and at page 32, Table 5. It is respectfully submitted that no new matter has been added by virtue of the present amendment.

B. Double Patenting

In the Office Action, the Examiner provisionally rejected claims 43-76 "on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46 and 52-54 of co-pending Application No. 11/224,785."

In response, as the obviousness type double patenting rejection is provisional, Applicants will consider the filing of Terminal Disclaimers to obviate the double-patenting rejection upon indication from the Examiner that the claims are otherwise allowable.

C. Rejection Under 35 U.S.C. § 112

In the Office Action, the Examiner rejected claim 76 under 35 U.S.C. 112, second paragraph, "as being indefinite". In making the rejection, the Examiner stated that "Claim 76 recites the limitation "said core" and "said membrane" in lines 2 and 3 of the claims", and "[t]here is insufficient antecedent basis for this limitation in the claim."

In response, claim 76 has been amended without prejudice to provide antecedent basis for the core and membrane terms of the claim. Therefore, the Examiner's is requested to remove the rejection of claim 76 under 35 U.S.C. 112, second paragraph.

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D. Rejection Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 43-45, 47-49, 51-53, 55-57, 59-61, 63-65, 67-69, 71-73 and 75 under 35 U.S.C. 102(a) and (e) as anticipated by Whitcomb (U.S. Patent No. 6,011,049). In making the rejection, the Examiner stated that "The disclosure is silent to the particular Cmax values however the concentrations of the metformin are identical to those of the instant claims." The Examiner further stated that "[i]t is the position of the Examiner that the formulations of [Whitcomb] would inherently possess these properties since the concentrations are identical and applicant has not provided any other defining features of the claims."

This rejection is traversed. It is respectfully submitted that Whitcomb fails in the very least to teach a controlled release oral dosage form which is suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof and which provides a mean Cmax as recited in claims 43 and 47. Further, it is respectfully submitted that Whitcomb only incidentally mentions a "controlled release formulation" at column 4, lines 35-38 and a "slow release form" at column 5, lines 30-34 of Whitcomb. Whitcomb fails to teach how such formulations are made, whether such formulations are suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof, and whether such formulations provide a mean Cmax as recited in claims 43 and 47. Furthermore, "controlled release" or "slow release" does not necessarily equal once a day dosing. For example, Wellbutrin SR® and Cardizem SR® are both extended formulations dosed twice a day. Therefore, one simply cannot extrapolate to the claimed formulations from the limited disclosure in Whitcomb.

The Examiner is reminded that to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326

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(C.C.P.A. 1981). *See also, In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

It is respectfully submitted that the Examiner has not met his burden of proof to make an inherency rejection as there is no indication in Whitcomb that the claimed Cmax of the present invention must be "necessarily present" in the formulations described in Whitcomb. Further, Whitcomb fails to even teach how such controlled release formulations are made. In addition, there is no indication in the Examples that Whitcomb even contemplates the use of metformin or a pharmaceutically acceptable salt thereof in a controlled release dosage form suitable for once-a-day administration, as recited in the present claims.

As Whitcomb does not expressly nor inherently teach the presently claimed invention, the Examiner is respectfully requested to withdrawal this rejection.

E. Rejection Under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 43-45, 47-49, 51-53, 55-57, 59-61, 63-65, 67-69, 71-73 and 75 under 35 U.S.C. §103(a) for obviousness over Whitcomb (U.S. Patent No. 6,011,049). In making the rejection, the Examiner stated that ". . . it would have been obvious to one or ordinary skill in the art to follow the teachings and suggestions of [Whitcomb] in order to provide an improved, easier method of treating diabetes", and "[i] would have been obvious to one or ordinary skill in the art to follow these teachings and suggestions with an expected result of a method of treating diabetes mellitus with a once-a-day formulation comprising a metformin compound."

In addition, the Examiner also rejected claims 46, 50, 54, 58, 62, 66, 70 and 74 under 35 U.S.C. 103(a) for obviousness over Whitcomb. In making the rejection, the Examiner stated that ". . . one of ordinary skill in the art would have been motivated to optimize the concentrations of the metformin in order to deliver and improve the method of treating diabetes mellitus", and "[i]t

would have been obvious to follow the disclosures of [Whitcomb] with an expected result of an optimized once-a-day dosage [form] capable of treating patients with NIDDM more effectively."

This rejection is traversed. As described above, Whitcomb fails to teach or suggest a controlled release oral dosage form which is suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof and which provides a mean Cmax as recited in claims 43 and 47. In fact, Whitcomb teaches away from once-a-day administration as demonstrated in column 4, lines 59-63, wherein the reference discusses the administered doses of metformin hydrochloride, and notes that "These can be given up to two times a day or more."

In addition, in the Examples, wherein Whitcomb exemplifies administration of the combinations of the active agents, there is no indication that metformin is in a controlled release form. Further in the study with metformin and troglitazone, Whitcomb indicates that 1000 mg metformin is administered in the study "BID" (twice a day), while 400 mg troglitazone is administered "QD" (once a day). See, e.g., col. 14, lines 21-24 of Whitcomb.

It is respectfully submitted that one of ordinary skill in the art would not be motivated to formulate a controlled release oral dosage form suitable for providing once-a-day oral administration of metformin or pharmaceutically acceptable salt thereof as recited in the present claims, in view of Whitcomb's description of the administration of metformin hydrochloride to be given up to two times a day or more, and Whitcomb's exemplification of the administration of 1000 mg on a twice a day basis.

As Whitcomb fails to teach or suggest the presently claimed invention, the Examiner is respectfully requested to withdrawal this rejection.

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F. Conclusion

It is respectfully submitted that in view of the actions taken an arguments presented, that this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

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PTO/SB/22 (12-04)
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OIPE IAP28 APR 20 2006 PATENT & TRADEMARK OFFICE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 300.1005CON2
Application Number 11/225,741	Filed September 13, 2005
For Controlled Release Metformin Compositions	
Art Unit 1618	Examiner Micah P. YOUNG

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

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

	Fee	Small Entity Fee	
☒ One month (37 CFR 1.17(a)(1))	$120	$60	$120
☐ Two months (37 CFR 1.17(a)(2))	$450	$225	$_____
☐ Three months (37 CFR 1.17(a)(3))	$1020	$510	$_____
☐ Four months (37 CFR 1.17(a)(4))	$1590	$795	$_____
☐ Five months (37 CFR 1.17(a)(5))	$2160	$1080	$_____

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

☒ A check in the amount of $550.00, $120.00 of which covers the fee is enclosed.

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

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

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-0552 . I have enclosed a duplicate copy of this sheet.

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

I am the

☐ applicant/inventor.

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

☒ attorney or agent of record. Registration Number 41,240

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

Signature	April 17, 2006
	Date
Robert J. Paradiso	212-736-1940
Typed or printed name	Telephone Number

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

☒ Total of 1 forms are submitted.

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

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04/20/2006 HDESTA1 00000021 11225741 120.00 OP
01 FC:1251

OIPE IAP28 APR 20 2006 PATENT & TRADEMARK OFFICE

UNITED STATES PATENT & TRADEMARK OFFICE

Re: Serial No.: 11/225,741

Application of: Chih-Ming Chen, et al.

Filed: September 13, 2005

For: **Controlled Release Metformin Compositions**

Examiner: Micah Paul Young

Art Unit: 1618

Docket No.: 300.1005CON2

Customer No.: 23280

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

April 17, 2006

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.56

Sir:

In accordance with the provisions of 37 C.F.R. § 1.97, Applicants hereby make of record the documents listed on the accompanying Form PTO-1449 (6 sheets) for consideration by the Examiner in connection with the examination of the above-identified patent application.

In accordance with 37 C.F.R. § 1.98(a)(2), copies of references "EN," "EP," "EQ," "ER," "ES," and "FC" through "FI" are enclosed. If it is determined that any of the listed references are not enclosed or have not been made of record in the parent application, the Examiner is requested to contact the undersigned so that copies may be forwarded.

Applicants note that references "AG," "DR," and "EA" on the enclosed form PTO-1449 were cited by the Examiner and made of record during prosecution of the parent application, U.S. Patent Application Serial No. 10/796,411.

04/20/2006 HDESTA1 00000021 11225741 180.00 OP
02 FC:1806

AURO BINDO EX. 1017 1/2

Applicants note that references "AI", "AM", "BS" and "DQ" on the enclosed Form PTO-1449 were cited in a first Opposition raised in connection with the corresponding Columbian Patent Application No. 03-036463. A copy of the first Opposition is enclosed as Appendix A. Applicants further note that references "AI", "AM" and "BS" on the enclosed Form PTO-1449 were cited in a second Opposition raised in connection with the corresponding Columbian Patent Application No. 03-036463. A copy of the second Opposition is attached as Appendix B. References "AI", "AM" and "BS" were considered by the Examiner in the grandparent application, U.S. Application Serial No. 09/705,630, filed November 3, 2000, now U.S. Patent No. 6,866,866, listed as reference "AA" on the enclosed Form PTO-1449.

Applicants also note that reference "CR" on the enclosed Form PTO-1449 was cited in the European Search Report issued in connection with corresponding European Patent Application No. 01991078. A copy of the Search Report is enclosed as Appendix C.

Applicants further note that references "AG", "DR", "ED" and "EN" on the enclosed Form PTO-1449 as well as Canadian patent No. 2,324493, corresponding to WO 99/47125 listed as reference "AM" on the enclosed Form PTO-1449, were cited by the Examiner in corresponding Canadian Patent Application No. 2,427,195.

Additionally, Applicants direct the Examiner's attention to reference "BT" on the enclosed Form PTO-1449. Reference "BT" was previously submitted in the parent case (U.S. Patent Application Serial No. 10/796,411) with the Information Disclosure Statement dated April 1, 2005, and was submitted under seal in the grandparent application, U.S. Application Serial No. 09/705,630, filed November 3, 2000, now U.S. Patent No. 6,866,866 (the '866 patent). As discussed in the Information Disclosure Statement dated February 28, 2003, of the '866 patent, reference "BT" is data from a biostudy which was performed using formulations prepared in accordance with U.S. Patent No. 6,099,859 (reference "AG" on the enclosed Form PTO-1449). It is noted that the exemplified formulations did not provide a T_{max} between 8-12 hours, except when the formulation prepared in accordance with Example 3 was administered at dinner. As set forth in the accompanying biostudy data, the mean T_{max} values for the Examples of the '859 were as follows: Example 1 (fasting) 4.67 hours (*See, e.g.*, pages 1 and 3 of the biostudy); Example 2 (fasting) 4.33 hours (*See, e.g.*, pages 10 and 12 of the biostudy); Example 2 (fed a.m.) 6.80 hours

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(*See, e.g.*, pages 13, 14 and 16 of the biostudy); Example 3 (fed a.m.) 6.67 hours (*See, e.g.*, pages 4 and 6 the biostudy); Example 3 (Fed p.m.) 9.67 hours (*See, e.g.*, pages 17 and 20 of the biostudy). Therefore, the only instance that the T_{max} was between 8-12 hours was Example 3 fed in the P.M. (at dinner).

In addition, pages 2, 5, 11, 15, 19 of the biostudy data includes plasma concentration v. time graphs and data for formulations prepared in accordance with Examples 1(fasting), 3 (fed), 2 (fasting), 2 (fed), and 3 (fed), respectively, of U.S. Patent No. 6,099,859; pages 8 and 9 of the biostudy data include plasma concentration v. time graphs and data for formulations prepared in accordance with Example 2 (fasting and fed) and Example 3 (fed a.m. and p.m.) of U.S. Patent No. 6,099,859; and pages 7 and 18 include plasma concentration v. time graphs and data for formulations prepared in accordance with Example 3 (fed a.m. and p.m.) of U.S. Patent No. 6,099,859.

Applicants also respectfully advise the Examiner of the following co-pending U.S. patent applications which are commonly assigned to the owners of the instant application:

U.S. Patent Application Serial No. 11/117,999, "Controlled Release Metformin Compositions," filed April 29, 2005, published on February 16, 2006 as U.S. Publication No. 2006/0034922, listed as reference "EK" on the enclosed Form PTO-1449;

U.S. Patent Application Serial No. 10/796,411, "Controlled Release Metformin Compositions," filed March 9, 2004, published on November 4, 2004 as U.S. Publication No. 2004/0219209, listed as reference "EG" on the enclosed Form PTO-1449;

U.S. Patent Application Serial No. 11/224,784, "Controlled Release Metformin Compositions," filed September 13, 2005, published on January 12, 2006 as U.S. Publication No. 2006/0008523, listed as reference "EJ" on the enclosed Form PTO-1449;

U.S. Patent Application Serial No. 10/442,692, "Biguanide formulations," filed May 20, 2003, published on March 18, 2004 as U.S. Publication No. 2004/0052848, listed as reference

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"EL" on the enclosed Form PTO-1449; and

U.S. Patent Application Serial No. 09/726,193, "Controlled Release Metformin Compositions," filed November 29, 2000, published on September 27, 2001 as U.S. Publication No. 2001/0024659, listed as reference "EM" on the enclosed Form PTO-1449.

It is respectfully requested that the references cited in the accompanying Form PTO-1449 (6 sheets) be considered and made of record.

This Information Disclosure Statement is being filed after a First Office Action but before a Final Office Action or Notice of Allowance. Pursuant to 37 C.F.R. § 1.98(c), a check for $180.00 is enclosed to cover the required fee. However, if it is determined that any additional fee is due or an overpayment has been made, the Examiner is authorized to charge said fee or credit said overpayment to our Attorney Deposit Account No. 50-0552.

Respectfully submitted,
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By _____
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APR 20 2006
PATENT & TRADEMARK OFFICE

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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
300.1005CON2	11/225,741
APPLICANTS: CHEN et al.	
FILING DATE: September 13, 2005	GROUP: 1618

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	AA	6	8	6	6	8	6	6	03/15/05	Chen et al.	424	468	
	AB	6	7	9	0	4	5	9	09/14/04	Cheng et al.	424	468	
	AC	6	4	7	5	5	2	1	11/05/02	Timmins et al.	424	469	
	AD	6	2	8	4	2	7	5	09/01	Chen et al.	424	473	
	AE	6	2	7	0	8	0	5	08/01	Chen et al.	424	497	
	AF	6	0	9	9	8	6	2	08/00	Chen et al.	424	473	
	AG	6	0	9	9	8	5	9	08/00	Cheng et al.	424	464	
	AH	6	0	1	0	7	1	8	1/4/00	Al-Razzak et al.	424	464	
	AI	5	9	5	5	1	0	6	09/99	Moeckel et al.	424	464	
	AJ	5	8	5	8	3	9	8	1/12/99	Cho	424	450	
	AK	5	6	9	1	3	8	6	11/25/97	Inman et al.	514	691	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
													YES	NO
	AL	9	9	4	7	1	2	8	9/23/99	WO	A61K	9/24		
	AM	9	9	4	7	1	2	5	9/23/99	WO	A61K	9/20		
	AN	9	9	2	9	3	1	4	6/17/99	WO	A61K	31/155		
	AO	9	6	0	8	2	4	3	3/21/96	WO	A61K	31/155		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AP	*Physicians' Desk Reference* (54th Ed. 2000), pp. 831-835.
	AQ	Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371.
	AR	Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.
	AS	Dunn, Christopher J., et al., Metformin: A Review of its Pharmacological Properties and Therapeutic Use in Non-Insulin-Dependent Diabetes Mellitus, *Drugs* (1995), 49:721-747.
	AT	Karttunen, P., et al., The Pharmacokinetics of Metformin: A Comparison of the Properties of a Rapid-Release and a Sustained-Release Preparation, pp. 31-36.

EXAMINER _____ DATE CONSIDERED _____

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005CON2	SERIAL NO. 11/225,741
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: CHEN et al.	
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U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	BA	5	6	8	8	5	1	8	11/18/97	Ayer et al.	424	422	
	BB	5	6	7	4	9	0	0	10/7/97	Ubillas et al.	514	557	
	BC	5	6	6	8	1	1	7	9/16/97	Shapiro	514	55	
	BD	5	6	6	7	8	0	4	9/16/97	Wong et al.	424	472	
	BE	5	6	5	0	1	7	0	7/22/97	Wright et al.	424	473	
	BF	5	6	3	1	2	2	4	5/20/97	Efendic et al.	514	12	
	BG	5	6	2	9	3	1	9	5/13/97	Luo et al.	514	284	
	BH	5	6	1	4	5	7	8	3/25/97	Dong et al.	524	377	
	BI	5	5	9	1	4	5	4	1/7/97	Kuczynski et al.	424	486	
	BJ	5	5	4	5	4	1	3	8/13/96	Kuczynski et al.	424	473	
	BK	5	5	4	3	1	5	6	8/6/96	Roorda et al.	424	484	
	BL	5	5	1	2	2	9	3	4/30/96	Landrau et al.	424	449	
	BM	5	4	1	3	5	7	2	5/9/95	Wong et al.	604	892.1	
	BN	5	3	0	8	3	4	8	5/3/94	Balaban et al.	604	892.1	
	BO	5	1	8	5	1	5	8	2/9/93	Ayer et al.	424	473	
	BP	5	1	7	8	8	6	7	1/12/93	Guittard et al.	424	473	
	BQ	5	1	4	1	7	5	2	8/25/92	Ayer et al.	424	473	
	BR	5	1	2	0	5	4	8	6/9/92	McClelland et al.	424	473	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
													YES	NO
	BS	0	0	2	8	9	8	9	05/00	WO	A61K	353		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	BT	Andrx Pilot Biostudy Data (20 pages)

EXAMINER	DATE CONSIDERED

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U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	CA	5	1	1	0	5	9	7		5/5/92	Wong et al.	424	438	
	CB	5	0	9	1	1	9	0		2/25/92	Kuczynski et al.	424	473	
	CC	5	0	7	1	6	0	7		12/10/91	Ayer et al.	264	112	
	CD	5	0	5	5	3	0	6		10/08/91	Barry et al.	424	482	
	CE	5	0	2	4	8	4	3		6/18/91	Kuczynski et al.	514	255.06	
	CF	4	9	6	3	1	4	1		10/16/90	Eckenhoff	604	892.1	
	CG	4	8	9	2	7	3	9		1/9/90	Shah et al.	424	473	
	CH	4	8	6	5	5	9	8		9/12/89	Eckenhoff	604	892.1	
	CI	4	8	5	1	2	2	9		7/25/89	Magruder et al.	424	457	
	CJ	4	7	8	3	3	3	7		11/8/88	Wong et al.	424	468	
	CK	4	7	7	7	0	4	9		10/11/88	Magruder et al.	424	457	
	CL	4	7	0	4	1	1	8		11/3/87	Eckenhoff	424	438	
	CM	4	6	9	2	3	3	6		9/8/87	Eckenhoff et al.	424	468	
	CN	4	6	2	7	8	5	0		12/9/86	Deters et al.	604	892.1	
	CO	4	6	2	4	8	4	7		11/25/86	Ayer et al.	424	467	
	CP	4	6	1	5	6	9	8		10/7/86	Guittard et al.	604	892.1	
	CQ	4	6	1	2	0	0	8		9/16/86	Wong et al.	604	892.1	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	CR	0	0	1	2	0	9	7		03/09/00	WO (A1)	A61K	31/64		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	CS	Chio, C. Sustained-Release Drug Delivery Systems Remington: the Science and Practice of Pharmacy, 1995, Mack Publishing Company, Easton PA pp 1660-1669

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	DA	4	6	0	9	3	7	4		9/2/86	Ayer	424	473	
	DB	4	5	8	7	1	1	7		5/6/86	Edgren et al.	424	473	
	DC	4	5	2	2	6	2	5		6/11/85	Edgren	424	473	
	DD	4	1	1	1	2	0	1		9/5/78	Theeuwes	424	473	
	DE	4	0	8	8	8	6	4		5/9/78	Theeuwes et al.	219	121.71	
	DF	4	0	8	0	4	7	2		3/21/78	Bohuon	514	555	
	DG	4	0	7	7	4	0	7		3/7/78	Theeuwes et al.	424	427	
	DH	4	0	6	3	0	6	4		12/13/77	Saunders et al.	219	121.7	
	DI	4	0	3	6	2	2	8		7/19/77	Theeuwes	424	473	
	DJ	4	0	3	4	7	5	8		7/12/77	Theeuwes	424	427	
	DK	4	0	0	8	7	1	9		2/22/77	Theeuwes et al.	424	427	
	DL	3	9	5	7	8	5	3		5/18/76	Bohuon	560	143	
	DM	3	9	5	2	7	4	1		4/27/76	Baker	424	405	
	DN	3	9	1	6	8	9	9		11/4/75	Theeuwes et al.	424	424	
	DO	3	8	4	5	7	7	0		11/5/74	Theeuwes et al.	424	427	
	DP	3	6	2	1	0	9	7		11/16/71	Scott	424	247	
	DQ	3	1	7	4	9	0	1		03/23/65	Sterne	514	635	
	DR	5	9	2	2	7	6	9		07/13/99	Barelli et al.	514	616	

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

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FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1005CON2	SERIAL NO.: 11/225,741
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): CHEN et al.	
		FILING DATE: September 13, 2005	GROUP: 1618

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	EA	5	9	1	4	3	2	6	06/22/99	McCarty et al.	514	188	
	EB	6	1	1	7	4	5	1	09/12/00	Kumar	424	465	
	EC	5	1	0	0	6	6	9	03/31/92	Hyon, et al.	424	426	
	ED	6	0	5	1	5	9	7	04/18/00	Zhang et al.	514	414	
	EE	5	8	3	7	3	7	9	11/17/98	Chen et al.	424	465	
	EF	6	0	5	6	9	7	7	05/02/00	Bhagwat et al.	424	488	
	EG	20	04	02	19	2	0	9	11/04/04	Chen et al.			
	EH	20	06	00	08	5	2	6	01/12/06	Chen et al.			
	EI	20	06	00	08	5	2	4	01/12/06	Chen et al.			
	EJ	20	06	00	08	5	2	3	01/12/06	Chen et al.			
	EK	20	06	00	34	9	2	2	02/16/06	Cheng et al.			
	EL	20	04	00	52	8	4	8	03/18/04	Cheng et al.			
	EM	20	01	00	24	6	5	9	09/27/01	Chen et al.			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
													YES	NO
	EN	2	2	5	1	4	3	0	2/28/00	CA	A61K	31/44		
	EO													

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	EP	E.K. Kastrup: "Anidiabetic Agents," DRUG FACTS AND COMPARISONS, 1999, St. Louis, pp 635-642
	EQ	Physicians' Desk Reference, "Glucophage XR," 56th edition, pages 1080-1086
	ER	Physicians' Desk Reference, "Glucophage," 52nd edition, pages 795-800
	ES	STN Registry Search for Metformin

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FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1005CON2	SERIAL NO.: 11/225,741
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): CHEN et al.	
		FILING DATE: September 13, 2005	GROUP: 1618

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*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	FA	6 1 9 1 1 6 2	02/20/01	Byrd et al.	514	440	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	FB							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	FC	Approval letter from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 000, October 13, 2000
	FD	Approved Label for Glucophage/Glucophage XR, NDA 21-202, Supplement 000, October 13, 2000
	FE	Approval letter on labeling revision from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 003, January 8, 2002
	FF	Approval letter on formulation revision from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 008, April 11, 2003
	FG	Approval letter on labeling revision from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 011, March 19, 2004
	FH	Approval letter on labeling revision from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 013, March 19, 2004
	FI	Approval letter on labeling revision from Center for Drug Evaluation and Research to Bristol-Myers Squibb Company on NDA 21-202, Supplement 001, April 19, 2001
	FJ	Approved Label For Glucophage/Glucophage XR NDA 21-202, Supplement 013, March 19, 2004
	FK	Approved Label for Glucophage/Glucophage XR NDA 21-202, Supplement 011, March 19, 2004
	FL	Approved Label for Glucophage/Glucophage XR NDA 21-201, Supplement 008, labeling revision, April 11, 2003
	FM	
	FN	
	FO	
	FP	

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(51) Cl. Int./Int. Cl.: A61K 31/4439, A61K 9/38, A61K 9/30, A61P 1/04

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(54) Titre : PREPARATION D'OMEPRAZOLE
(54) Title: OMEPRAZOLE FORMULATION

(57) Abrégé/Abstract
A pharmaceutical composition of omeprazole for oral administration is described which consists essentially of: (a) a tableted core component containing a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and (b) a single layer of coating on said core which comprises a layer of an enteric coating agent.

CA 02251430 1998-10-21

ABSTRACT

A pharmaceutical composition of omeprazole for oral administration is described which consists essentially of:

(a) a tabletted core component containing a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and

(b) a single layer of coating on said core which comprises a layer of an enteric coating agent.

CA 02251430 2003-12-01

OMEPRAZOLE FORMULATION

BACKGROUND OF THE INVENTION:

The present invention relates to a stable formulation of omeprazole. It is well known that omeprazole is sensitive to acidic conditions and after contact with an acid, omeprazole will degrade and will not function in its intended manner. Initially, alkaline materials were added to a core of omeprazole and later an enteric coating was applied over the core to prevent the omeprazole from contacting the acidic pH conditions of the stomach. This approach is satisfactory if the product is administered within a short time after it is manufactured but if the product is stored under ambient conditions, the acidic residue of the enteric coating appears to degrade the omeprazole before it is administered to a patient. To solve this problem, the prior art has used a separate layer of a coating agent to coat a pellet core which contains omeprazole and an alkaline material which is thereafter coated with the enteric coating. This technique is described in U.S. 4,786,505.

This dual layer coating technique requires the application of two separate functional coating operations which increases the length of the manufacturing process and the cost of the product. The applicants have surprisingly discovered a coating system which avoids the need to use a coating layer to separate the omeprazole core from the enteric coating layer in an omeprazole dosage form. The separate coating system is based on the combined use of an enteric coating agent which is applied to cores of omeprazole as a suspension in an suitable solvent.

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SUMMARY OF THE INVENTION

The present invention provides a novel dosage form of omeprazole which consists essentially of:

(a) a compressed tablet core made from a granulation comprising a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and

(b) a single layer of coating on said core which comprises a layer of an enteric coating agent.

Accordingly, it is a primary object of this invention to provide a pharmaceutical dosage formulation of omeprazole which is stable upon prolonged storage, is stable when administered to a patient and is capable of providing the desired therapeutic effect.

It is also an object of this invention to provide a pharmaceutical dosage form of omeprazole which is bioequivalent to dosage forms of omeprazole which have an intermediate layer of an inert coating material.

It is also an object of this invention to provide a stable dosage form of omeprazole which may be produced without the need to provide an intermediate coating layer that separates the omeprazole containing core from the enteric coating layer.

In a broad aspect, then, the present invention relates to a stable pharmaceutical dosage formulation for oral administration consisting essentially of: (a) a tablet-in-tablet core consisting essentially of 5 to 70 weight percent based on the total weight of the core of omeprazole, 0.1 to 5 weight percent based on the total weight of the core of a surface active agent, 25 to 50 weight percent based on the total weight of the core of a filler, 0.1 to 10 weight percent based on the total weight of the core of a binder and 20 to 60 weight percent based on the total weight of the core of a pharmaceutically acceptable alkaline agent, wherein the alkaline agent is selected from the group consisting of lysine and arginine; and (b) a coating layer

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surrounding the core that consists of an enteric coating agent, 10 to 50 weight percent based on the total weight of the coating layer of an inert processing aid and 0 to 40 weight percent based on the total weight of the coating layer of a plasticizer wherein the coating layer is applied directly to the omeprazole containing core without a separating layer between the omeprazole containing core and coating layer.

In another broad aspect, then, the present invention relates to a method for preparing a stable oral pharmaceutical dosage formulation which consists essentially of: (a) forming a tablet core consisting essentially of 5 to 70 weight percent based on the total weight of the core of omeprazole, 0.1 to 10 weight percent based on the total weight of the core of a binder, 25 to 50 weight percent based on the total weight of the core of a filler, 0.1 to 5 weight percent based on the total weight percent of the core of a surface active agent and 20-60 weight percent based on the total weight of the core of an alkaline agent wherein the alkaline agent is selected from the group consisting of lysine and arginine; and (b) applying a coating layer to the tablet core that surrounds the tablet core and consists of an enteric coating agent, 10 to 50 weight percent, based on the total weight of the coating layer of an inert processing aid and 0 to 40 weight percent based on the total weight of the coating layer of a plasticizer wherein the coating layer is applied directly to the omeprazole containing tablet core without a separating layer between the omeprazole containing tablet core and coating layer.

The objects and essence of the invention will become apparent from a review of the appended specification.

DETAILED DESCRIPTION OF THE INVENTION

The omeprazole formulation of the invention is preferably based on a compressed tablet core formed from a granulation which comprises omeprazole, a surface active agent, a filler, an alkaline material and a binder.

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The omeprazole may comprise from 5 to 70wt% and preferably 10 to 30wt% of the granulation.

The surface active agent may be any pharmaceutically acceptable, non-toxic surfactant. Suitable surface active agents include sodium lauryl sulfate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 and the like.

The surface active agent may be present at a level of from 0.1 to 5wt% and preferably 0.20 to 2.0wt% based on the total weight of the granulation.

The alkaline material is selected from the group consisting of the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid and aluminum/magnesium compounds such as $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O)$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$ where n is a whole integer of 2 or more. In addition the alkaline material may be selected from lysine or arginine or from the group consisting of antacid materials such as aluminum hydroxides, calcium hydroxides, magnesium hydroxides and magnesium oxide. The alkaline agent may be present at a level of 10 to 80wt% based on the total weight of the granulation, depending on the relative strength of the alkaline material. If the preferred arginine is employed, a level of from 20 to 60wt% and preferably 30 to 55wt% based on the weight of the granulation may be employed.

The binder may be any pharmaceutically acceptable, non-toxic pharmaceutically acceptable binder. The binder is preferably a water soluble polymer of the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and the like. A water soluble binder is preferred which is applied from an aqueous medium such as water at a level of from 0.1 to 10wt% and preferably from 0.25 to 7.5wt% of binder based on the total weight of the granulation.

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A filler is used as a granulation substrate. Sugars such as lactose, dextrose, sucrose, maltose, or microcrystalline cellulose and the like may be used as fillers in the granulation composition. The filler may comprise from 25 to 50wt% and preferably 20 to 40wt% based on the total weight of the granulation.

A tablet disintegrant may be added which comprises corn starch, potato starch, croscarmelose sodium, crospovidone and sodium starch glycolate in an effective amount. An effective amount which may be from 3 to 7wt% based on the total weight of the granulation.

The enteric coating agent may comprise an acid resisting material which resists acid up to a pH of above about 5.0 or higher which is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, Eudragit™ L (poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit™ S (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B) and mixtures thereof. For example Eudragit™ L100-55 is a 100% polymer solids product while the Eudragit™ L30-55 product is a 30%w/w/ aqueous dispersion of the polymer. The enteric coating agent may also include an inert processing aid in an amount from 10 to 50wt% and preferably 20 to 40wt% based on the total weight of the acid resisting component and the inert processing aid. The inert processing aids include finely divided forms of talc, silicon dioxide, magnesium stearate etc. Typical solvents which may be used to apply the acid resisting component-inert processing aid mixture include isopropyl alcohol, acetone, methylene chloride and the like. Generally the acid resistant component-inert processing aid mixture will be applied from a 5 to 20wt% of acid resisting component-inert processing aid mixture based on the

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total weight of the solvent and the acid resistant component-inert processing aid.

The enteric coating may optionally comprise a plasticizer. Suitable plasticizers include acetyl triethyl citrate, dibutyl phthalate, tributyl citrate, triethyl citrate, acetyl tributyl citrate, propylene glycol, triacetin, polyethylene glycol and diethyl phthalate. The amount of plasticizer can vary, but will typically be present in the amount of 0 to 40% w/w based upon the weight acid resisting component of the coating, and more preferably about 10-20% w/w based upon the weight of the acid resisting component.

The granulation is formed by contacting the alkaline agent, the omeprazole, the surface active agent and the binder with a medium which may comprise any low viscosity solvent such as water, isopropyl alcohol, acetone, ethanol or the like. When fluids such as water are employed, this will usually require a weight of fluid which is about three times the weight of the dry components of the coating composition.

After the granulation is formed and dried, the granulation is tabletted and the tablets are directly coated with the enteric coating agent. A color imparting agent may be added to the enteric coating agent mixture or a rapidly dissolving seal coat containing color may be coated over the enteric coating agent layer provided that the seal coat is compatible with and does not affect the dissolution of the enteric coating layer. The rapidly dissolving seal coat may comprise Opadry™ pink which comprises approximately 91wt% hydroxypropyl methylcellulose (E-6), color and 9wt% polyethylene glycol which is applied as a 8-15%w/w solution in purified water. In addition the color may be provided as "Chromateric" which is available from Crompton & Knowles. This product contains water, talc, TiO_2, triethyl citrate, propylene glycol, synthetic red iron oxide, potassium sorbate, xanthan gum, sodium citrate

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and synthetic yellow iron oxide. If desired, conventional sugar based seal coats may be used which contain FDA certified dyes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

Granulation.

A granulation containing omeprazole is formed in fluid bed coater using a top spray granulation forming suspension containing micronized omeprazole, 5%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose, 95%w/w of the total amount of L-arginine and sodium starch glycolate. The formulation for making the granulation has the following composition:

povidone, USP (Plasdone™ K30)	100.0g
sodium starch glycolate	100.0g
sodium lauryl sulfate, NF/USP	6.0g
microcrystalline cellulose (Avicel™ PH101)	965.6g
L-arginine, USP/FCC	1020.0g
omeprazole, USP (micronized)[1]	340.0g
purified water, USP	1100.0g

[1] 95% of the particles exhibit a particle size of less than 15 microns

Tabletting.

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with glyceryl monostearate:

omeprazole granules	118.0g
glyceryl monostearate (EASTMAN™ 600P)	6.0g

Tabletting tools: 0.2812"
target weight : 124mg/tab
target hardness : 7Kp
LOD of granules : less than 3%

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Enteric coating.

An enteric coating was applied to prepare enteric coated tablets as follows:

omeprazole tablets (prepared above)	124.0g
hydroxypropyl methylcellulose phthalate 55	14.7g
talc	4.2g
acetyl tributyl citrate	2.9g
acetone	148.0g
isopropyl alcohol	148.0g

The solid coating materials were dissolved in the acetone and isopropyl alcohol and this solution was coated onto the omeprazole tablets using a perforated pan.

Seal coat:

A seal coat was applied to the enteric coated tablets as follows:

Enteric coated tablet	146.0g
Opadry™ TT pink	4.5g
Water	450.0g

The seal coat was applied onto the enteric coated omeprazole tablets using a perforated pan coater.

EXAMPLE 2

Granulation.

A granulation containing omeprazole is formed in fluid bed coater using a top spray granulation forming suspension containing micronized omeprazole, 5.00%w/w of the total amount of L arginine, polyvinyl pyrrolidone, polysorbate 80 and purified water which is sprayed onto

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a mixture of microcrystalline cellulose and 95.0%w/w of the total amount of L-arginine. The formulation for making the granulation has the following composition:

	mg/tablet
povidone, USP (Plasdone™ K30)	5.88
polysorbate 80 (Tween™ 80)	0.58
L-arginine, USP/FCC	60.0
omeprazole, USP (micronized)[2]	20.0
microcrystalline cellulose (Avicel™ PH102)	25.54
purified water, USP	n/a

[2] 95% of the particles exhibit a particle size of less than 15 microns

Tabletting.

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with crospovidone XL, then with glyceryl monostearate:

omeprazole granules	112.0mg
glyceryl monostearate (EASTMAN™ 600P)	6.8mg
crospovidone XL	16.2mg

Tabletting tools: 0.2812"
target weight : 135mg/tab
target hardness : 7Kp
LOD of granules : less than 3%

Enteric coating.

An enteric coating was applied to prepare enteric coated tablets as follows:

omeprazole tablets (prepared above)	135.0mg
Eudragit™ L30D-55	14.0mg
color (Chromateric)	7.0mg
1M NaOH (pH adjuster to pH 5.0)qs	na
Purified water qs	na

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The solid coating materials were dispersed in the water and this mixture was coated onto the omeprazole tablets using a perforated pan.

EXAMPLE 3

Granulation.

A granulation containing omeprazole is formed in fluid bed coater using a top spray granulation forming suspension containing micronized omeprazole, 5.0%w/w of the total amount of L-arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose and 95.0%w/w of the total amount of L-arginine. The formulation for making the granulation has the following composition:

	mg/tablet
povidone, USP (Plasdone™ K30)	5.0
sodium lauryl sulfate	0.3
L-arginine, USP/FCC	60.0
omeprazole, USP (micronized)[3]	10.0
microcrystalline cellulose (Avicel™ PH102)	24.7
purified water, USP	n/a

[3] 95% of the particles exhibit a particle size of less than 15 microns

Tabletting.

The granulation is tabletted into tablets containing 10mg of omeprazole by first mixing the omeprazole granules with sodium starch glycolatye and then with glyceryl monostearate:

omeprazole granules	100.0mg
glyceryl monostearate (EASTMAN™ 600P)	5.0mg
sodium starch glycolate	5.0mg

Tabletting tools: 0.2812"
target weight : 110mg/tab
target hardness : 7Kp
LOD of granules : less than 3%

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Enteric coating.

The tablets were coated with the same enteric coating that was applied to the tablets in Example 2.

EXAMPLE 4

Granulation.

A granulation containing omeprazole is formed in fluid bed coater using a top spray granulation forming suspension containing micronized omeprazole, 5.0%w/w of the total amount of L arginine, polyvinyl pyrrolidone, sodium lauryl sulfate and purified water which is sprayed onto a mixture of microcrystalline cellulose, crospovidone XL and 95.0%w/w of the total amount of L-arginine. The formulation for making the granulation has the following composition:

	mg/tablet
povidone, USP (Plasdone™ K30)	5.88
polysorbate 80	0.60
L-arginine, USP/FCC	60.0
omeprazole, USP (micronized)*	20.0
crospovidone XL	5.88
microcrystalline cellulose	25.54
purified water, USP	n/a

* 90% of the particles exhibit a particle size of less than 15 microns

Tabletting.

The granulation is tabletted into tablets containing 20mg of omeprazole by first mixing the omeprazole granules with glyceryl monostearate:

omeprazole granules	117.9mg
glyceryl monostearate (EASTMAN™ 600P)	6.1mg

Tabletting tools: 0.2812"
target weight : 124mg/tab
target hardness : 7Kp
LOD of granules : less than 3%

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Enteric coating.

The tablets were coated with the same enteric coating that was applied to the tablets in Example 1.

EXAMPLE 5

The granulation of Example 1 was prepared and tabletted into tablets containing 20.0mg of omeprazole. These tablets were coated as follows:

Enteric coating.

An enteric coating was applied to prepare enteric coated tablets as follows:

omeprazole tablets (prepared above)	126.00mg
Eudragit™ L30D-55	17.00mg
1M NaOH (pH adjuster to pH 5.0)qs	na
acetyl tributyl citrate	1.70mg
talc	3.80mg
polysorbate 80	1.50mg
Purified water qs	na

The coating polymer was diluted with water and the other coating materials were added. This mixture was coated onto the omeprazole tablets using a perforated pan. A seal coat was applied using the procedure of Example 1.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A stable pharmaceutical dosage formulation for oral administration consisting essentially of:

(a) a tabletted core consisting essentially of 5 to 70 weight percent based on the total weight of the core of omeprazole, 0.1 to 5 weight percent based on the total weight of the core of a surface active agent, 25 to 50 weight percent based on the total weight of the core of a filler, 0.1 to 10 weight percent based on the total weight of the core of a binder and 20 to 60 weight percent based on the total weight of the core of a pharmaceutically acceptable alkaline agent, wherein the alkaline agent is selected from the group consisting of lysine and arginine; and

(b) a coating layer surrounding the core that consists of an enteric coating agent, 10 to 50 weight percent based on the total weight of the coating layer of an inert processing aid and 0 to 40 weight percent based on the total weight of the coating layer of a plasticizer wherein the coating layer is applied directly to the omeprazole containing core without a separating layer between the omeprazole containing core and coating layer.

2. A pharmaceutical composition of omeprazole as defined in claim 1, wherein the alkaline agent is arginine.

3. A pharmaceutical composition of omeprazole as defined in claim 1, wherein the enteric coating agent is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, and co-polymerized methacrylic acid/methacrylic acid methyl esters.

4. A pharmaceutical composition of omeprazole as defined in claim 1 wherein the surface active agent is a sodium lauryl sulfate.

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5. A method for preparing a stable oral pharmaceutical dosage formulation which consists essentially of:

(a) forming a tablet core consisting essentially of 5 to 70 weight percent based on the total weight of the core of omeprazole, 0.1 to 10 weight percent based on the total weight of the core of a binder, 25 to 50 weight percent based on the total weight of the core of a filler, 0.1 to 5 weight percent based on the total weight percent of the core of a surface active agent and 20-60 weight percent based on the total weight of the core of an alkaline agent wherein the alkaline agent is selected from the group consisting of lysine and arginine; and

(b) applying a coating layer to the tablet core that surrounds the tablet core and consists of an enteric coating agent, 10 to 50 weight percent based on the total weight of the coating layer of an inert processing aid and 0 to 40 weight percent based on the total weight of the coating layer of a plasticizer wherein the coating layer is applied directly to the omeprazole containing tablet core without a separating layer between the omeprazole containing tablet core and coating layer.

6. The dosage formulation as defined in claim 1 wherein the core consists essentially of 10 to 30 weight percent based upon the total weight of the core of omeprazole; 0.20 to 2.0 weight percent based upon the total weight of the core of the surface active agent; 0.25 to 7.5 weight percent based upon the total weight of the core of the binder; 20 to 40 weight percent based upon the total weight of the core of the filler and 30-55 weight percent based upon the total weight of the core of the alkaline agent.

7. The dosage formulation as defined in claim 1 wherein the coating layer consists of 20 to 40 weight percent based upon the total weight of the coating layer of the inert processing aid and 10 to 20 weight percent based upon the

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total weight of the coating layer of the plasticizer.

8. The method as defined in claim 5 wherein the core consists essentially of 10 to 30 weight percent based upon the total weight of the core of omeprazole; 0.20 to 2.0 weight percent based upon the total weight of the core of the surface active agent; 0.25 to 7.5 weight percent based upon the total weight of the core of the binder; 20 to 40 weight percent based upon the total weight of the core of the filler and 30 - 55 weight percent based upon the total weight of the core of the alkaline agent.

9. The method as defined in claim 5 wherein the coating layer consists of 20 to 40 weight percent based upon the total weight of the coating layer of the inert processing aid and 10 to 20 weight percent based upon the total weight of the coating layer of the plasticizer.

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APPENDIX A

Optimum **Competition Regulations, Industrial Property and Foreign Trade**

Head of,

NEW CREATIONS DIVISION

SUPERINTENDENCE OF INDUSTRY AND COMMERCE

Reference:	File No. 03-036463
Case:	Opposition to patent application **"CONTROLLED RELEASE METFORMIN COMPOSITIONS"**
Applicant:	**ANDRX CORPORATION**
Opponent:	**PROCAPS S.A.**

Published in Industrial Property Gazette No. 544 of September 30, 2004

I, Luis Fernando Rincón Cuellar, attorney-at-law with professional card No. 113438 of National Council if the Judiciary, acting as agent of society PROPCAPS S.A. that was set up according to the laws in force in the Republic of Colombia, and central office in Barranquilla, Colombia, by means of the present writing I declare that, on due time and according to the orders received by said

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company, I file opposition against the grant of patent for the invention named **"CONTROLLED RELEASE METFORMIN COMPOSITIONS"**, applied for **ANDRX CORPORATION**, and ask you to declare well founded this opposition and in consequence, and refuse to grant the patent requested.

2. LEGITIMATE INTEREST

Head of,

NEW CREATIONS DIVISION

SUPERINTENDENCE OF INDUSTRY AND COMMERCE

Reference:	File No. 03-036463
Case:	Opposition to patent application **"CONTROLLED RELEASE METFORMIN COMPOSITIONS"**
Applicant:	**ANDRX CORPORATION**
Opponent:	**PROCAPS S.A.**

Published in Industrial Property Gazette No. 544 of September 30, 2004

I, Luis Fernando Rincón Cuellar, attorney-at-law with professional card No. 113438 of National Council if the Judiciary, acting as agent of society PROPCAPS S.A. that

was set up according to the laws in force in the Republic of Colombia, and central office in Barranquilla, Colombia, by means of the present writing I declare that, on due time and according to the orders received by said company, I file opposition against the grant of patent for the invention named "**CONTROLLED RELEASE METFORMIN COMPOSITIONS**", applied for **ANDRX CORPORATION**, and ask you to declare well founded this opposition and in consequence, and refuse to grant the patent requested.

2. LEGITIMATE INTEREST

According to article 42 of Decision 486 of the Andean Community of Nations, year 2000, within the terms stipulated by the law, I declare legitimate interest of the company I represent provided that the alleged application does not fulfil the requirements according to law as it will be analysed later, and if it is granted, it would affect the commercialisation that the company I represent intends with the pharmaceutical presentation manufactured based on Metformin molecule. Therefore, I respectfully request that Office to consider the present opposition within the administrative proceedings handled by the Superintendence.

3. FACTS

3.1 The application object of the present opposition was filed on May 2, 2003, claiming priority under US09/705,630 of 11/03/2000, and US09/705,625 of 11/03/2000, which beginning date in national phase was June 3, 2003, with international publication No. WO02/36100 of May 10, 2002 that was published in Colombia in the Industrial Property Gazette No. 544 of September 30, 2004, with the number NP.348 (page 344).

3.2 Colombian application No. 03/036463, object of the present opposition, according to claims 1 to 42, comprises a controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of at least one suitable antihyperglycemic drug or a pharmaceutically acceptable salt thereof and a controlled release carrier, said dosage form being suitable for providing once-a-day oral administration of the agent or pharmaceutically acceptable salt thereof, wherein the dosage form provides a mean time

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to maximum plasma concentration(Tmo) of the agent from 5.5 to 7.5 hours after the administration. Furthermore claims that said drug is metformin or a pharmaceutically acceptable salt thereof. Furthermore claims that the controlled release oral dosage form exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the drug is released after 2 hours; 10-45% of the drug is released after 4 hours; 30-90% of drug is released after 8 hours; not less than 50% of the drug is released after 12 hours; not less than 60% of the drug is released after 16 hours; and not less than 70% of the drug is released after 20 hours. The application claims a method of treatment and the use of said controlled release oral dosage form.

3.3 First of all, it must be noticed that claims 1 to 44 that characterize the state of the art, are general and do not define typical characteristics to define them as an invention. From said claims, it is not

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possible to establish an inventive advance, capable of a study over patentability requirements. Furthermore, claim 44 refers to a use, and according to legislation, Decision 486 of the Andean Community of Nations, Article 14.- *"The Member Countries shall grant patents for inventions, whether goods or processes, in all areas of technology, that are new, involve an inventive step, and are industrially applicable"*, uses are not excluded from patent. Only goods and procedures are patentable matter.

3.4 Similarly, in claim 43 it is also intended to be claimed a method for a therapeutic treatment. Decision 486 of the Andean Community of Nations, clearly states in its article 20 that: *"The following shall not be patentable: ...d) diagnostic, therapeutic, and surgical methods for the treatment of humans or animals"*. From the above, as may readily be deduced, the aim of the present application cannot be considered object for patent in Colombia.

3.5 Decision 486 of the Andean Community of Nations states in its article 14 that: *"The Member Countries shall grant patents for inventions, whether goods or*

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processes, in all areas of technology, that are new, involve an inventive step, and are industrially applicable". The present application lacks of industrial applicability, provided that, as it was already demonstrated in the above paragraph, a method for treatment is being claimed, and they are not industrially applicable first al all, because a result is not obtained by means of the use of natural materials or forces; and secondly, it can not be repeated provided that, once the predicted media are used, the result is not always the same. Therefore, the aim of the present invention does not fulfill with the industrially applicable requirement.

3.6 Article 14 of Decision 486 of the Andean Community of Nations refers that inventions for patent must be new and have inventive step. Now then, before the date of priority of the present application, next documents that affect novelty and inventive step are found:

- D1: US 3,174,901 (03-23-65)
- D2: WO 00/28989 (05-25-00)
- D3: WO 99/47125 (09-23-99)

- D4: US 5,955,106 (09-21-99)

3.7 Document D1 affects the NOVELTY of the present application, provided that it previously reveals a composition of dimethylbiguanide (Metformin). See page 1, lines 13 - 20. This document defines a novel method of treating diabetes by oral administration as well as to the pharmaceutical composition useful thereof that contains as active ingredient a dimethyl biguanide (Metformin). According to such previous document, said pharmaceutical composition contains as active ingredient a dimethyl biguanide (Metformin) that can be prepared in different pharmaceutical forms. Similarly, in page 3, lines 70 - 75 is defined that the ingredients of the composition can be mixed in proper proportion and filled into hard or soft gelatin capsules. Alternatively, the components can be mixed, granulated with suitable lubricants and tableted; and that conventional or sustained released tablets can be prepared by methods known to the formulation art. It is clear that this document reveals the matter claimed in the application object of remission. Therefore, the present application,

according to D1, lacks NOVELTY requirement, provided that what is alleged is already published, a long time before the priority for Colombian application was filed.

3.8 On the other hand, document D2 reveals a novel composition, particularly a composition of modified released that comprises an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefore, and its use in medicine, especially its use for the treatment of Diabetes Mellitus. This document D2 reveals that the modified release is a sustained release, for example providing effective release of active agents over a time period of up to 26 hours, typically in the range of 4 to 24 hours, according to page 3, lines 3 to 5. It is clear that this document reveals the matter claimed in the application object of remission. Therefore, the present application, according to D2, lacks NOVELTY requirement, provided that what is alleged is already published, a long time before the priority for Colombian application was filed.

3.9 Similarly, any person in the trade with average skills in the technical field concerned is capable to design a controlled release oral dosage form to obtain the plasmatic concentration - time profiles. Therefore, the present application, in the light of document D1 combined with document D2, lacks INVENTIVE STEP requirement, provided that what is alleged is obtainable from the state of the art.

3.10. Reference D3 clearly connects, according to page 1, lines 3 to 7, a controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as Metformin or Buformin or a pharmaceutically acceptable salt thereof. Reference D3 reveals a controlled or sustained released formulation for an antihyperglycemic drug that can provide continuous an non-pulsating therapeutic levels of an antihyperglycemic drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period. Similarly, document D3 reveals in claims 26 and 27 a dissolution profile similar to the one claimed in the present application. Therefore,

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document D3 affects the NOVELTY of what is claimed in the present application that is being object of opposition. Consequently, Colombian application that is being object of opposition reveals the same object already mentioned in document D3. Therefore, this oral dose of controlled released to reduce the glucose levels is not NOVEL in the light of document D3.

3.11. Furthermore, and as it is already known in the state of the art, many techniques have been used to produce pharmaceutical forms of controlled release doses and extended for maintaining therapeutic serum levels in the drugs (see document D2). Therefore, what is set out in the claims of Colombian application No. 03-036463 is obviously derived from documents D1 and D2 combined with document D3, demonstrating that this is obvious for person in the trade with average skills in the technical field concerned. Therefore, combining the knowledge revealed in applications D1 and D2 together with D3, directly affects the requirement of INVENTIVE STEP of the Colombian application.

3.12. However, document D4 concerns pharmaceutical compositions containing Metformin as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances. Particularly, the object of document D4 was to design an improved pharmaceutical composition containing Metformin as an active substance. Particularly, administering form would have to contain Metformin as an active substance, possibly with a high content of active substance and a retardant, and the retardant causes a controlled released of the active substance. Therefore, it demonstrates a controlled release oral dosage form to reduce the glucose levels by means of the use of Metformin, then, in the light of document D4, the present application object of opposition, lacks its NOVELTY.

3.13. Similarly, a controlled release oral dosage form that produce a maximum plasmatic concentration of metformin at a desired time before administration can be evidently derived combining documents D1, D2, D3 and D4.. That is so certain that the application object of opposition by itself has stated in page 1

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that lots of techniques in the state of the art have been used to produce controlled release oral dosage pharmaceutical forms or extended to maintain the levels of therapeutic serum in the drugs. Therefore, what is contained in the claims of Colombian application No. 03-036463, is evidently derived from the previous art contained in combined form, in documents D1 to D4. Then, it is demonstrated that this is obvious to any person with average skills in the technical field concerned. Therefore, combining the knowledge that is contained in applications D1 to D4 altogether, directly affects the INVENTIVE STEP requirement of the present Colombian application.

3.14. Consequently, and according to the above, it is derived that Colombian application No. 03-036463 cannot try a patent monopoly, provided that the application does not fulfil the necessary TREE requirements for protection.

3.15. Consequently, in reference to the pretended application, it is true that:

3.15.1 **LACKS OF NOVELTY**: according to Decision 486 of the Andean Community of Nations, Article 16.- *"An invention may be deemed new when not included in the state of the art.*

The state of the art comprises everything that has been made available to the public by written or oral description, use, marketing, or any other means prior to the filing date of the patent or, where appropriate, of the priority claimed." On priority date, November 3, 2000, the matter looking for protection contained in the claim chapter was already known, provided that it was already part of the previous art, based on documents D1, D2, D3 and D4.

3.14.2. **LACKS OF INVENTIVE STEP**: according to Decision 486 of the Andean Community of Nations, Article 18.- *"An invention shall be regarded as involving an inventive step if, for a person in the trade with average skills in the technical field concerned, the said invention is neither obvious nor obviously derived from the state of the art."* On filing date, May 2, 2003 and based on combination of documents D1 to D4, it is possible to deduce a controlled release

oral dosage form to reduce the serum glucose levels, in human patients.

3.14.3. **LACKS OF INDUSTRIAL APPLICABILITY**: according to Decision 486 of the Andean Community of Nations, Article 14 states that *"The Member Countries shall grant patents for inventions, whether goods or processes, in all areas of technology, that are new, involve an inventive step, and are industrially applicable."* The present application lacks of industrial applicability provided that, as it was demonstrated, what is claimed is a method for treatment. And a method for treatment does not have industrial applicability, first at all because a result is not obtained by means of the use of matters or forces from nature; and second, it cannot repeated given that once the predicted media have been used, the same result cannot be always obtained. Therefore, the object of the present invention does not fulfill the industrial applicability requirement.

3.15. According to the above, it is possible to deduce that the application and what is claimed are not patentable matters provided that they are opposite to

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article 14 of Decision 486 of the Andean Community of Nations that states *"The Member Countries shall grant patents for inventions, whether goods or processes, in all areas of technology, that are new, involve an inventive step, and are industrially applicable."* The alleged application does not fulfill the tree patentability requirements.

3.16. Consequently, if the required registry were granted, it would induce the monopoly of a product that does not fulfill the fundamental requirements demanded by Decision 486.

3.17. By all the above, I kindly request you to declare well founded the present opposition and to refuse registration of the patent **"CONTROLLED RELEASE METFORMIN COMPOSITIONS"**, applied by **ANDRX CORPORATION,** Colombian application published in the Industrial Property Gazette No. 544, under NP. 348 (page 344).

4. EVIDENCES

Arranged according to the regulations in force, I request you to consider the next documents as evidences:

- D1: US 3,174,901 (03-23-65)
- D2: WO 00/28989 (05-25-00)
- D3: WO 99/47125 (09-23-99)
- D4: US 5,955,106 (09-21-99)

5. FUNDAMENTAL POINTS OF LAW

I base this observation in the next legal regulations:

5.1 Numeral 1 of article 586 of Commercial Code

5.2 Article 42 of Decision 486 of Commission of the Cartagena Agreement.

5.3. The others concordant regulations.

6. ANNEXES

To the corresponding effects, I annex the documents mentioned in evidences chapter the same way as the next documents:

6.1. Payment receipt issued by the Special Fund of that Superintendence, in which it is a fact that the correspondent fees for opposition procedures have been paid.

6.2. Copy of the opposition for the applicant's transfer.

6.3. Power of Attorney

7. NOTICES

For notices purpose according to article 50 of Decree 01, 1984, my client and I will receive the notices in Superintendence secretary's office or in my attorney's office address in Calle 119 A No. 53-99 in Bogotá.

Yours faithfully,

LUIS FERNANDO RINCÓN CUELLAR

Id card No. 79.532.186 of Bogotá

P.C.A. 113.438 of S.C.J.

APPENDIX B

Traductora e Intérprete Oficial
Inglés-Español / Español-Inglés,
Según Resolución 0526 de 11 de Junio de 2002
emitida por el Ministerio de Justicia y del Derecho
Meryam Adam J.
CC 52 252 613 Bté

TRANSLATION OF A DOCUMENT COPY FROM SPANISH TO ENGLISH BY MERYAM ADAM J. Tel: +571 6917116

At the upper right hand side: "Superintendence of Industry and Commerce; Registration No. 03036463 00010005; Folios: 3; Date (illegible portion): 2005-03-29, 13:51:46; Procedure: 011 PCT-Patent 379 NACI Phase 329 Suppl.; Department: 2020 Department of New Creations"

"Mister
Superintendent of Industry and Commerce
E.S.D. (En su Despacho – Delivered to your office)

REF:	**FILE 03-036-463**
REQUESTED TITLE:	**"Continuous Release Metformin Compositions"**
PUBLISHED:	**Journal 544 issued 30-09-2004, number 348.**
PRIORITY:	**US 09/705,630 of 03/11/2000**
	US 09/705,625 of 03/11/2000
REQUESTER:	**ANDRX CORPORATION**
AGENT:	**JUANITA ACOSTA GÓMEZ**
PROCEDURE:	**OPPOSITION UPHOLDING**

JOSÉ LUIS REYES VILLAMIZAR, identified as below my signature, acknowledged agent for the opponent for the aforementioned procedure, within the terms of the requested extension, I hereby ratify and uphold the arguments of the main opposition document, also registered within the legal term before such entity.

I. RATIFICATION

I reiterate to your Office our request to deny patent benefits for all claims included in the file of reference, based on the arguments established in the opposition document of December 28th 2004, where it was explained that the pharmaceutical

composition evidenced in Colombian request CO-03-036-463, lacks innovation and inventive level by virtue of publications from dates prior to the priority request date, such as the American US 5,955,106 patent and international application WO 99/47125, for these documents reveal controlled release compositions that involve an antihyperglycemic drug such as Metformin, along with binding agents and absorption enhancers, and a semi-permeable membrane covering the nucleus.

II. SUPPLEMENTARY INFORMATION

I request this Office also take into account the international application WO 00/28989 published May 25th, 2000 (mentioned in the opposition document), and equivalent to the Colombian request which is being processed by procedure no. 99-071-573 published in Journal 515, for it proves the lack of innovation and inventive level of the Colombian request being processed, for it not only refers to a **modified release** pharmaceutical composition with two active substances – one of which may be **Metformin** -, but demonstrates that not only should the possibility of administering these types of drugs on an individual basis in formulations that allow their modified release be known, but also the possibility of administering both of them in the same release scheme, whereas release of at least one of the two agents were possible.

In addition to the above, it must be said that the description in the Colombian request 99-071-573 evidences certain alternatives or possibilities to achieve the release of the drug (s) involved in the composition, as follows:

a. ..."Modified release is a retarded release, boosted or sustained, preferably retarded, conveniently achieved by use of a gastric acid - resistant formulation, such as an enteric formulation, as a tablet coated with a polymer resistant to gastric acids, for example Eudragit L100-55. Other polymers resistant to these acids include ethacrylates, methylhydroxypropyl cellulose phthalate, .."(pages 3 and 4).

b. "The tablet with such coating may be a single layer tablet, where all active substances are mixed before compression to form a tablet or a multi-layer tablet, by which each active substance is within a discreet layer held in the shape of the compressed tablet. These discreet layers may be disposed of as required to provide modified or unmodified release of each active substance" (page 4).

c. Sustained release is provided by using a sustained release matrix, usually in a tablet shape, such as jointing matrixes, or not jointing matrixes or eroded matrixes. (page 4).

d. Sustained release may also be achieved by using a tablet coated with a semi-permeable membrane; or using a multiple-layer tablet, where each active substance is formulated jointly or as a separate layer, for example, as a tablet with a matrix, whereby the other layers provide additional control for the sustained release of one or any of the two active substances. (page 5).

e. The Example 2 illustrated in page 14 reveals the sustained release by use of a semi-permeable membrane of a composition involving an insulin sensitizer and a biguanide. The semi-permeable membrane consists of:

Eudragit RS30D (30% aqueous dispersion)	90% p/p
Triethyl Citrate	1% p/p
Talcum	9% p/p

This membrane is applied to one or two-layer tablets , each one with 4mg or 8mg of a composite (I) and 500, preferable 1000mg or 1500mg of metformin. HCl

As evidenced, there are many types of formulations conducive to sustained release of one or more active substances, among which the release by use of a semi-permeable membrane, fact that allows a notorious ratification that the Colombian request being processed 03-036-463, lacks innovation and inventive level, therefore, I request the denial of the indicated request, and that the file be placed into order consequently, due to evident non-compliance with the provisions of Articles 14, 16, 18, 19, 20-d and 21 of Ruling 486 of 2000.

Mr. Superintendent,

(Signature)
JOSÉ LUIS REYES VILLAMZIAR
Id Card No. 79.152.473 issued in Usaquén
Professional Card No. 44655 issued by C.S.J. (Consejo Superior de la Judicatura – Higher Judicature Council)"

I hereby declare that this is a true translation of one (1) document; that I am well acquainted with the English and Spanish languages; that I am an Official Translator and Interpreter accredited by Resolution number 0036 issued by the Universidad Nacional de Colombia on July 5th, 2.000 and Resolution 0526 issued by the Ministry of Justice on June 11th, 2.002, and that my signature is registered at the Ministry of Foreign Affairs of Colombia.

Bogotá, May 3, 2005

Traductora e Intérprete Oficial
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Según Resolución 0526 de 11 de Junio de 2002
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CC 52 252 613 B...

MERYAM ADAM J.
ID Card No. 52.252.613 issued in Bogotá

Traductora e Intérprete Oficial
Inglés-Español / Español-Inglés,
Según Resolución 0526 de 11 de Junio de 2002
Emitida por el Ministerio de Justicia y del Derecho
Meryam Adam J.
CC 52 252 613 Bta

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At the upper right hand side: "Superintendence of Industry and Commerce; Registration No. 03036463 00000004; Folios: 49; Date (AMD NT:YMD): 2004-12-28, 12:40:35; Procedure: 011 PCT-Patent 379 NACI Phase 379 400 Opposition; Department: 2020 Department of New Creations". In handwriting: TRANSFER"

Seal of the Superintendence of Industry and Commerce

"SOLE OPPOSITION FORMAT

2000-12

1. Opposition to:

X Invention Patent

_ Utility Model Patent

_ Industrial Design

_ Trace scheme for Integrated circuits

_ Trademark of Products or Services

_ Collectiva marks

_ Certification marks

_ Commercial Slogan

2. Published Request

File no. 03.036.463

Requester: ANDRX CORPORATION

Agent: Juanita Acosta Gómez

Title of the new creation or name of the sign: **"CONTINUOUS RELEASE METFORMIN COMPOSITIONS"**; Journal: 544 of 30-09-2004, Page 344 – Publication no. 348.

3. Opposition submitted by:

Opponent:

Name: **Tecnoquímicas S.A.**

Address: **Calle 23 # 7-39**

Tel.: **(092) 882.55.55**

Fax: **(092) 883.88.59**

Domicile: **Cali, Valle**

Identification:

_ ID Card

X Tax Identification no.

_ Foreign ID Card

_ Other

Number: 890.300 466-5

Representative or Agent (74):

Name: **José Luis Reyes Villamizar**

Address: **Cra. 17 # 88-23, Of. 205**

Tel.: **621.26.31**

Email: **info@reyes-abogados.com**

Fax: **621.25.42**

Domicile: **Bogotá, D.C.**

Identification:

X ID Card

_ Tax Identification no.

_ Foreign ID Card

_ Other

Number: 79.152.473 issued in Usaquén

4. Grounds of the opposition:

Grounds: Failure to comply with patentability requirements (Title II, Chapter I, Ruling 486, 2000). Violation of articles 14 (invention patents must be new, have an inventive level and must be subject to industrial application), 16 (an invention is

deemed new when it is not obvious or derived in any evident way of the technique's condition), 18 (an invention has an inventive level when it is not obvious for a person who is knowledgeable in the subject), 19 (an invention is subject to industrial application when its purpose may be produced or used in any type of industry), 20-d (therapeutic or surgical methods for human or animal treatment, as well as diagnosis methods applied to human beings or animals), 21 (the products or procedures already patented and involved with the technique's condition, according to Article 16 of this Ruling, shall not be subject to a new patent solely for having attributed a use different than the one originally included in the initial patent).

Justification: The pharmaceutical composition of this request lacks innovation and inventive level, should we take into account what was disclosed in the American patent US 5,955,106, the international application WO 99/47125, for this document reveals controlled release compositions that involve an antihyperglycemic drug such as Metformin, along with binding agents and absorption enhancers, and a semi-permeable membrane covering the nucleus.

FOLLOWING PAGE:

5. Payment receipt No. 37880145 (opposition) **Date:** 22-12-2004
37880145 (Extension) **Date:** 22-12-2004

6. Annexes:

X receipt of payment for administrative charges

X Powers of attorney, if any

X Evidence of the opposition grounds

X Certificate of Incumbency and Legal Representation of the parties should they be a legal person

_ Documents supporting legitimate interest, should it be deemed necessary.

X Copy of the opposition for transfer to the requester

7. NAME: JOSÉ LUIS REYES VILLAMIZAR

SIGNATURE: (Signature)

ID Card No. 79.152.473; Professional Card No. 44655"

FOLLOWING PAGE:

"Mister
Superintendent of Industry and Commerce
E.S.D. (En su Despacho – Delivered to your office)

REF:	**FILE 03-036-463**
REQUESTED TITLE:	**"Continuous Release Metformin Compositions"**
PUBLISHED:	**Journal 544 issued 30-09-2004, number 348.**
PRIORITY:	**US 09/705,630 of 03/11/2000**
	US 09/705,625 of 03/11/2000
REQUESTER:	**ANDRX CORPORATION**
AGENT:	**JUANITA ACOSTA GÓMEZ**
PROCEDURE:	**OPPOSITION SUBMITTAL**

JOSÉ LUIS REYES VILLAMIZAR, of legal age, identified as below my signature, practicing lawyer, holder of Professional Card no. 44655 issued by the C.S.J. (Consejo Superior de la Judicatura – Higher Judicature Council), acting as agent of the Company **TECNOQUÍMICAS S.A.**, as per the provisions of Articles 42 and those following Ruling 486 of 2000 of the Andean Nation Community, I hereby respectfully request you process the following

I. REQUEST

Deny patent benefits to the request included in file **03-036-463**, due to failure to comply with patentability requirements referred to in Articles 14, 16, 18, 19, 20-d and 21 of Ruling 486 of the Andean Nation Community, based on the de facto and lawful grounds explained below.

II. LEGITIMATE INTEREST

TECNOQUÍMICAS S.A. has legitimate interest in filing this opposition, for the eventual assignment of the request would restrict without justification the use of certain substances and pharmaceutical compositions, which lack innovation and inventive level, in detriment of their legitimate commercial interests and of free trade.

III. GROUNDS FOR THE OPPOSITION

3.1 Colombian request 03-036-463 lacks innovations and inventive level, taking into account the following arguments:

3.1.1. First, I inform this Office that compositions involving an **antihyperglycemic medication such as Metformin** or an acceptable salt there from and a vehicle or **holder of controlled release** already exist, as per publication in 1999-09-21 of the American patent US 5,955,106, the title of which is "Pharmaceutical Preparation Containing metformin and a process for producing it", which reveals pharmaceutical compositions involving **Metformin** as an active substance and a hydrocolloid-forming **agent** as a **retardant**[1], and optionally auxiliary pharmaceutical substances.

In addition, the oral dosage form of controlled release disclosed in claim 29 of the request being processed in which metformin is proportioned at least as a controlled release tablet, lacks innovation and inventive level, whereas each tablet contains:

a) a nucleus including: i) Metformin or a pharmaceutically acceptable salt there from; ii) Option of a binding agent; and iii) Option of an absorption enhancer.
b) a membrane coating covering the nucleus; and
c) at least one pathway through the membrane.

The above is proven if we take into account the examples of the American patent

[1] The retardant agent enables controlled release of the active substance, as per description in column 1, lines 33 to 38 of US 5,955,106.

US 5,955,106, for these cases describe compositions in a tablet shape including:

a) a nucleus that includes: Metformin Hydrochloride; hydrocolloid-forming agents or "retarders", binding agents such as cellulose derivatives, dextrins, starches and other polymers based on carbohydrates and polyvynilpyrrolidone; lubricants and flow regulators.
b) a coating film or membrane.

I must add at this point that claim 29 is evidently undetermined and lacks precision, for it intends to achieve exclusivity for a controlled release tablet that includes Metformin, along with other excipients, without revealing or indicating, at least in the claim chapter, which is the excipient, its proportions, weights and other properties that should characterize such formulation, which is why its assignment would cover the use of any binding agent, absorption enhancer and any membrane coating.

As for the release time (T_{max}) of the Colombian request being processed, which corresponds to 5.5 to 7.5 hours after administration, we may say that this range had already been revealed and covered in the description of column 5, lines 30 to 32 of US 5,955,106 patent mentioned numerous times, for this document states that: "the retarded tablets as per the invention, release metformin in a controlled manner in a 0.5-10 hour time period, preferably more than 4 hours".

3.1.2. The international application WO 99/47125 published September 23rd, 1999, proves once more the lack of innovation and inventive level of the Colombian request 03-036-463, as follows:

International publication WO 99/47125 (23-09-1999)	Colombian request 03-036-463
Claim 1:	**Claim 29:**

One controlled release pharmaceutical tablet includes: a) a nucleus including: i) an antihyperglycemic drug; ii) Option of a binding agent; and iii) Option of an absorption enhancer and b) a semi-permeable membrane coating covering the nucleus; and c) at least one pathway through the membrane.	the oral dosage form of controlled release disclosed in claim 1, in which metformin is proportioned at least, as a controlled release tablet, whereas each tablet contains: a) a nucleus including: i) Metformin or a pharmaceutically acceptable salt there from; ii) Option of a binding agent; and iii) Option of an absorption enhancer. b) a membrane coating covering the nucleus; and c) at least one pathway through the membrane. **Claim 30:** The oral dosage form of controlled release of claim 29, whereas such membrane is semi-permeable.
Claim 2: The controlled release pharmaceutical tablet of Claim 1, in which the antihyperglycemic drug is a biguanide.	**Claim 2:** the oral dosage form of controlled release disclosed in claim 1, in which the antihyperglycemic drug is a biguanide
Claim 3: The controlled release pharmaceutical tablet of Claim 2, in which the antihyperglycemic drug is Metfomin or a pharmaceutically acceptable salt there from.	**Claim 3:** The oral dosage form of controlled release of Claim 2, in which the biguanide is Metfomin or a pharmaceutically acceptable salt there from.

Claim 26: The controlled release pharmaceutical tablet, as defined in Claim 1, and which displays the following dissolution profile, which was tested according to USP in the type 2 device at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 buffer phosphate) and at 37^0C: - after 2 hours 0-25% of the drug is released; - after 4 hours 10-45% of the drug is released; - after 8 hours 30-90% of the drug is released; - after 12 hours at least 50% of the drug is released; - after 16 hours at least 60% of the drug is released; - after 20 hours at least 70% of the drug is released;	**Claim 7:** The oral dosage of controlled release of Claim 1, which displays the following dissolution profile, which was tested according to USP in the type 2 device at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 buffer phosphate) and at 37^0C: - 0-30% of the drug is released after 2 hours; - 10-45% of the drug is released after 4 hours; - 30-90% of the drug is released after 8 hours; - at least 50% of the drug is released after 12 hours; - at least 60% of the drug is released after 16 hours; - at least 70% of the drug is released after 20 hours;
Claim 27: The controlled release pharmaceutical tablet, as defined in Claim 1, and which displays the following dissolution profile, which was tested according to USP in the type 2 device at 75 rpm in 900 ml of	**Claim 8:** The oral dosage of controlled release of Claim 1, which displays the following dissolution profile, which was tested according to USP in the type 2 device at 75 rpm in 900 ml of simulated intestinal

simulated intestinal fluid (pH 7.5 buffer phosphate) and at 37°C: - after 2 hours 0-15% of the drug is released; - after 4 hours 20-40% of the drug is released; - after 8 hours 45-90% of the drug is released; - after 12 hours at least 60% of the drug is released; - after 16 hours at least 70% of the drug is released; - after 20 hours at least 80% of the drug is released;	fluid (pH 7.5 buffer phosphate) and at 37°C: - 0-25% of the drug is released after 2 hours; - 20-40% of the drug is released after 4 hours; - 45-90% of the drug is released after 8 hours; - at least 60% of the drug is released after 12 hours; - at least 70% of the drug is released after 16 hours; - at least 80% of the drug is released after 20 hours;

After a simple comparison among the quoted documents, it may be evidenced that the controlled release oral dosage form, disclosed in the request being processed involving the nucleus containing Metformin as an active substance, a binder, and absorption enhancer and a semi-permeable membrane covering such nucleus, lacks innovation and inventive level, for the international publication WO 99/47125 mentioned before, already revealed pharmaceutical compositions with controlled release of an antihyperglycemic agent such as Metformin or its pharmaceutically acceptable salt, along with binding agents and absorption enhancers, covered with a semi-permeable membrane.

The aforementioned is – without need for further explanation – the lack of innovation and inventive level covered by a characterization of a controlled release

composition of the antihyperglycemic agent Metformin.

I must also indicate that observing the comparative table, regarding claim 26 vs. claim 7, and claim 27 vs. claim 8, it is logical and evident to deem that if the pharmaceutical composition is similar, not to say identical, the dissolution profiles of the revealed compositions in international application WO 99/47125, mentioned so may times before, and in the Colombian request 03-036-463 being processed, should also be similar, even identical.
This being the situation, the pharmaceutical composition and the dissolution profiles of the request in reference, had already been revealed in the technical condition, which is the basis of the violation of requirements 16 and 18 of Ruling 486.

3.1.3. International application WO 00/28989 called "Pharmaceutical Composition for modified release of an insulin sensitiser and another antidiabetic agent", published May 25th, 2000, also proves lack of innovation and inventive level of the Colombian request being processed, because it not only refers to a pharmaceutical composition with **modified release** and two active substances – one of which may be **Metformin** -, it also allows to prove that not only the possibility of administering these types of drugs on an individual basis in formulations that permit their modified release be known, but also the possibility of administering them both under the same releasing scheme.

It is once more proven that Metformin, and its possibility of being formulated in modified release compositions, belong to the aforementioned, which is proof of violation of the main patentability requirements of Ruling 486.

In addition to the above, I inform this Office that should we consider the lessons of American Patent US 5,955,106, international application WO 99/47125 and international application WO 00/28989, we may establish once more, the lack of

innovation and inventive level of the Colombian request being processed, for these documents reveal characteristics that altogether allow a more or less knowledgeable person in this subject to determine the obviousness of the protection pretenses by means of a patent in this particular case.

3.1.4. The controlled release mechanism revealed in the request being processed is within the technical condition, which is why its use in the formulation lacks inventive level.

There are currently several products in the market, which are administered orally and supply the drug in a controlled or sustained manner. Conventional pharmaceutical forms release their active substances immediately within an absorption pack. Regarding the non-immediate release systems, efforts are made particularly to alter the active substance's release; there are supply systems for medications or pharmaceutical forms with non-immediate release, which are widely known and are listed below:

retarded release
sustained release; a)**Controlled release**, b) extended release
release in one specific site
release in the receiver

It is known that the retarded or late release system uses repeated and intermittent emissions of the medication from one or more immediate release units, within a dosage form. On the other hand, the sustained release form includes medication supplies that produce a slow release during an extended period. If the system accomplishes to maintain a constant medication level in the blood or in the targeted tissue, it is considered a ***controlled release*** system; if this is not accomplished, but instead extends the length of the action compared with

conventional supply, it is considered an extended release system[2].

This is why it is clear for anyone knowledgeable in pharmaceutical processes, that the release proportion obtained by a drug in the stomach depends on the release process used, and on the ingredients used to produce the pharmaceutical preparation. It is known that the drug's blood levels start to increase from the moment the medication is administered, and in the case of retarding action preparations, although they do not remain constant, they do remain within a therapeutically appropriate interval. The speed of release and, therefore, the blood levels achieved, are largely dependant on the ingredients used during the process.

It is also well known that repeated action tablets and capsules and enteric covered pills enable a time-measured release by virtue of the presence of such cover which acts a barrier. The enteric covers remain intact in the stomach, but then dissolve and release the pharmaceutical form contents once in the small intestine, and their purpose is to retard the release of the active substances that were inactive in the stomach or that may cause nausea or bleeding due to irritation of the gastric mucosa.

The use of polymers is very common in the pharmaceutical industry as formulation auxiliaries for the preparation of compressed tablets covered with substances that do not dissolve in the stomach. It is common to use polymers within tablets' composition as disintegrators that aid the release of the active substances once the enteric layer is gone.

All the above enable us to conclude that the possibility of formulating an antihyperglycemic such as Metformin or its pharmaceutically acceptable salt, along with a controlled release vehicle, such as a semi-permeable membrane covering the nucleus, is not new to someone somewhat knowledgeable in this subject; on

[2] REMINGTON FARMACIA, XVII Edition, Editorial Médica Panamericana, 1987. Chapter 92 p. 2240-2242

the contrary, it's nothing more than the application of the foundations and acquired knowledge pertaining to the state of the art.

3.1.5. On the other hand, please notice that the Colombian request being processed refers to a "TREATMENT METHOD" in Claim 43, for not insulin-dependent diabetes mellitus (NIDDM), which includes the oral administration once a day of a controlled release form containing 850-1700mg of Metformin.

As it is well known, therapeutic methods are forbidden according to Article 20, letter d) of Ruling 486 of 2000, for it indicates word by word: "Therapeutic or surgical methods for human or animal treatment, as well as diagnosis methods applied to human beings or animals, are not subject to patent".

Even if this were possible, the innovation requirement should be fulfilled, which in fact is violated if taken into account that the international application WO99/47125, reveals controlled release tablets with 850mg of Metformin HCl, which provide continuous therapeutic levels of an antihyperglycemic drug to an animal or a human being in need of treatment.

3.1.6. Claim 44 of the request being processed, focused on the use of a composition, is unacceptable with respect to Ruling 486.
It is unacceptable as it is, the pretension to attribute exclusiveness on a "Use", a category that has not been included in the "Products or Procedure" concept set forth in Article 14 of Ruling 486 of 2000. The above also, is consistent with SIC's reiterated interpretation of this issue.

Finally, I reiterate that even if the uses or therapeutic methods were allowed in our milieu, these should be forced to comply with the material requirements for patentability, especially, in this case, with those related to Inventive Level and Industrial Application.

Although we have already referred to the former, we may take notice immediately that the latter in impossible to fulfill, since *industrial reproduction* of separate, combined or sequential medication use for treatment of certain pathologies pertains to the medical professional and not to the industrial activities.

Being this as it is, and based on the arguments explained throughout this document, I respectfully reiterate the request by which your office abstain from granting the requested patent and that the respective file be placed into order consequently.

IV. LEGAL GROUNDS

As legal grounds of this opposition, I invoke Chapter I, Articles 14, 16, 18, 19, 20-d and 21 (Patentability Requirements), Article 51 (Claims) and Article 42 (Oppositions) of Ruling 486 of 2000.

V. REQUEST FOR EXTENSION TO UPHOLD THE OPPOSITION

As per the provision of Article 42, numeral 2 of Ruling 486, I hereby request your Office an additional 60 day extension to uphold his opposition. For this purpose, I am annexing the proof of payment for such request.

VI. PROOF

I request you take into account the following, without prejudice of those which may be submitted once the requested extension has expired and of those this Office may consider unofficially:

6.1 American Patent US 5,955,106

6.2 First page and claims of International application WO 99/47125

6.3 First page and claims of International application WO 00/28989

VII. ANNEXES

For the purpose of the corresponding process, I hereby annex the following

documents to this communication

1. Certificate of Incumbency and Legal Representation of Tecnoquímicas S.A.
2. Power of Attorney to act.
3. Proof of payment of the opposition processing administrative charges.
4. Proof of payment to support extension request referred to in Article 42, numeral 2 of Ruling 486.
5. Copy to transfer to the requester.
6. Those mentioned in the proof paragraph.

VIII. NOTICES

The undersigned shall receive notices at the Secretariat of his Office or in my Office, located at Carrera 17 # 88-23, Office 205, Fax (1) 621.25.42 of this city. Tecnoquímicas S.A. shall receive them at their Secretariat of their Office or at their headquarters located at Calle 23 # 7-39 in Cali.

Mister Superintendent
(Signature)
JOSÉ LUIS REYES VILLAMIZAR
ID Card No. 79.152.473 (Usaquén)
Professional Card no. 44655 issued by C.S.J."

I hereby declare that this is a true translation of one (1) document; that I am well acquainted with the English and Spanish languages; that I am an Official Translator and Interpreter accredited by Resolution number 0036 issued by the Universidad Nacional de Colombia on July 5th, 2.000 and Resolution 0526 issued by the Ministry of Justice on June 11th, 2.002, and that my signature is registered at the Ministry of Foreign Affairs of Colombia.

Bogotá, May 3, 2005

Traductora e Intérprete Oficial
Inglés-Español / Español-Inglés
según Resolución 0036 de [illegible] de 2002
emitida por el Ministerio de [illegible]
Meryam A.

MERYAM ADAM J.
ID Card No. 52.252.613 issued in Bogotá

Traductora e Intérprete Oficial
Inglés-Español / Español-Inglés,
Según Resolución 0526 de 11 de Junio de 2002
emitida por el Ministerio de Justicia y del Derecho
Meryam Adam J.
CC 52.252.613 Bta

TRANSLATION OF A DOCUMENT COPY FROM SPANISH TO ENGLISH BY MERYAM ADAM J. Tel: +571 6917116

Seal on the upper right hand side of the document: "Superintendence of Industry and Commerce"

"2020 Requirement No. 12638
Bogotá, D.C.

In handwriting: "JAG 25-04-05"

Doctor
Darío Cárdenas Navas
Agent

REFERENCE:	PCT Registration No.	03-36463
	Procedural stage	011
	Event	379
	Procedure	440
	Folios	033

Based on the provisions of article 43 of Ruling 486 (an arrow points out towards Ruling 486 from the following handwritten notation: "Another Opposition") issued by the Andean Community Commission (Comisión de la Comunidad Andina), you are hereby notified that the opposition submitted by Doctor José Luis Reyes Villamizar, acting as Agent of Tecnoquímicas S.A., (The name of the Company has been circled in writing) fulfills all formal requirements established by the law upon its submittal.

In compliance thereof, you are granted sixty (60) working days following the date of this requirement's notice date, to validate your arguments and submit evidence.

Notification of this requirement has been served as per numeral 5.2, letter e) of chapter fifth, title first of Sole Communication No. 10 issued in 2001.

(Signature)
ALIX CARMENZA CÉSPEDES DE VERGEL
Chief of the Department of New Creations

This requirement was notified by establishment in date list, April 22nd, 2005."
202021

In writing at the end of the page: "ALERT! Defence Expires: July 21st, 2005; *Copy of transfer Opposition 1 "Tecnoquímicas S.A." annexed + Supplement of March 29th, 2005". Illegible signature.

At the end of the page: Downtown Branch: Carrera 13 # 27-00 Pisos 2, 5, 7 y 10; CAN Branch: Tr. 40A # 38-50; Tel.: 3820840; Fax: 382 2695; Line 9800-910 165. Web: www.sic.gov.co; email: info@sic.gov.co; Bogotá, D.C. – Colombia.

I hereby declare that this is a true translation of one (1) document; that I am well acquainted with the English and Spanish languages; that I am an Official Translator and Interpreter accredited by Resolution number 0036 issued by the Universidad Nacional de Colombia on July 5th, 2.000 and Resolution 0526 issued by the Ministry of Justice on June 11th, 2.002, and that my signature is registered at the Ministry of Foreign Affairs of Colombia.

Bogotá, May 3, 2005

Traductora e Interprete Oficial
Inglés-Español / Español-Inglés,
Según Resolución 0526 de 11 de Junio de 2002
emitida por el Ministerio de Justicia y del Derecho
Meryam Adam J.
CC 52 252 613 Btá

MERYAM ADAM J.
ID Card No. 52.252.613 issued in Bogotá

APPENDIX C

European Patent Office

SUPPLEMENTARY PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 01 99 1078

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 00/12097 A (ANDRX PHARMACEUTICALS, INC) 9 March 2000 (2000-03-09) * the whole document * * page 10, line 1 - page 11, line 20 * * examples * * claims * * claims 1,26 * -----	1-44	A61K9/24 A61K9/22 A61K9/28 A61K9/30 A61K9/36 A61K9/32 A61K31/155 A61K31/17 A61K31/175 A01N37/52 A01N47/28

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

INCOMPLETE SEARCH

The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
Munich	23 May 2005	Luangkhot, N

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C20)

AUROBINDO EX. 1017, 231

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 01 99 1078

Claim(s) searched completely:
2,3,29-30,40-43

Claim(s) searched incompletely:
1,4-28,31-39

Reason for the limitation of the search:

The expressions in claims 1,4-28,31-39 such as "wherein the dosage form provides a mean time to maximum plasma concentration of the agent from 5.5 to 7.5 hours after the administration", "which exhibits the following dissolution profile...", "which provides a width at ...", "which provides a mean AUC..." etc... do not delimit the scope of the protection to be sought and is rather to be construed as an attempt to define the invention by a result to be achieved, in particular it only amounts to claiming the underlying technical problem.

Furthermore the use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC since it is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to claims 2,3,29-30,40-43.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 99 1078

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

23-05-2005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0012097 A	09-03-2000	US 6099862 A	08-08-2000
		AT 269709 T	15-07-2004
		AU 749550 B2	27-06-2002
		CA 2341908 A1	09-03-2000
		DE 69918310 D1	29-07-2004
		EP 1107763 A1	20-06-2001
		WO 0012097 A1	09-03-2000
		US 6284275 B1	04-09-2001

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

AUROBINDO EX. 1017, 233

FORM PTO -1083

OIPE IAP28 APR 20 2006 PATENT & TRADEMARK OFFICE

Docket No.: 300.1005CON2
Date: April 17, 2006

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

In re application of: Chih-Ming CHEN, et al.
Serial No.: 11/225,741
Filed: September 13, 2005
For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

S i r:

Transmitted herewith is an **Amendment** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[ ] No fee for additional claims is required.
[X] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1) REMAINING AFTER AMENDMENT	(Col. 2) HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	LARGE ENTITY RATE	LARGE ENTITY FEE
FOR:								
TOTAL CLAIMS	39 Minus 34	=	5	x $	$		x $ 50	$ 250.00
INDEP. CLAIMS	Minus	=	0	x $	$		x $ 200	$ 00.00
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $	$		+ $ 360	$ 00.00

TOTAL: $ OR TOTAL: $250.00

[X] Also transmitted herewith are:
[X] Petition for extension under 37 C.F.R. 1.136
[X] Other:- Information Disclosure Statement with Form PTO-1449 and copies of references cited therein, and Appendix A, B and C

[X] Check(s) in the amount of **$550.00** is/are attached to cover:
[X] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for extension under 37 C.F.R. 1.136
[X] Other: Information Disclosure Statement Fee

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.
[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with sufficient postage to the United States Postal Service as "first class mail" in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450". on April 17, 2006.
DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: _____
Marina Krioutchkova

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.
11/225,741	09/13/2005	Chih-Ming Chen	300.1005CON	3874

23280 7590 12/16/2005

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 12/16/2005

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

AUROBINDO EX. 1017, 235

Office Action Summary	Application No.	Applicant(s)	
	11/225,741	CHEN ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

-- 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 _____.

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) 43-76 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) 43-76 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-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment of Papers Received: Preliminary Amendment dated 9/13/05.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 43-76 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-46,52-54 of copending Application No. 11/224,785. The claims of the instant invention are drawn to a controlled release oral dosage form comprising from 1000 to 2000 mg of metformin and a carrier. The claims recite specific mean maximum plasma concentration (Cmax) values are identical to the '785 claims. The difference between the instant claims and those of the '785 invention is that the '785 claims are silent to the particular in-vitro testing apparatus used, however these testing apparatuses are standard in the art and do not impart a particular patentable distinction on the actual; compound or formulation being tested. Since the results of the tests (Cmax) are identical for each set of claims although the instinct claims recite the particular test, it is the position of the Examiner that

claims are not patentably distinct and would serve as art over one another. A further difference is that the '785 claims recite a membrane surrounding a tablet core while the instant claims are silent to a particular form. However the claims of the instant invention are open to a controlled release layer/membrane and mention a core and membrane in latter independent claims. Again it is the position of the Examiner that the claims would act as opposing art over one another if issues and therefor are not patentably distinct.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

3. 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.

4. Claims 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 76 recites the limitation "said core" and "said membrane" in lines 2 and 3 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

6. 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 –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for

> patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 43-45,47-49,51-53,55-57,59-61, 63-65, 67-69, 71-73 and 75 are rejected under 35 U.S.C. 102(a and e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049). The claims are drawn to a once-a-day controlled-release dosage form comprising metformin and a control-releasing carrier. The metformin is present in concentrations from 1000 – 2000 mg and produces various Cmax values.

8. The '049 patent teaches a once-a-day oral metformin formulation for the treatment of diabetes mellitus (abstract, col. 5, lin. 7-24). The formulation comprises control-release carriers such as starch, gelatin and methylcellulose and takes the form of tablets or capsules (col. 5, lin. 27-33). The formulations comprise from 300 – 2000 mg of metformin (claims). The disclosure is silent to the particular Cmax values however the concentrations of the metformin are identical to those of the instant claims. It is the position of the Examiner that the formulations of the '049 would inherently possess these properties since the concentrations are identical and applicant has not provided any other defining features of the claims. With these things in mind, the disclosures of the '049 patent anticipate the claims.

Claim Rejections - 35 USC § 103

9. 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.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 43-45,47-49,51-53,55-57,59-61, 63-65, 67-69, 71-73 and 75 are rejected under 35 U.S.C. 102 (a and e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049).

As discussed above the '049 patent discloses a once-a-day formulation of metformin formulation comprising from 30 – 2000 mg of metformin. It is the position of the Examiner that the Cmax values would be inherent for the formulation since the concentrations are identical to those of the instant claims. It is further the position of the Examiner that the disclosures also obviate the instant claims, since the products of the art and the instant claims appear identical yet the disclosures are silent to the pharmokinetics. The Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28

U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. With these things in mind it would have been obvious to one of ordinary skill in the art to follow the teachings and suggestions of the '049 reference in order to provide an improved, easier method of treating diabetes mellitus. It would have been obvious to one of ordinary skill in the art to follow these teachings and suggestions with an expected result of a method of treating diabetes mellitus with a once-a-day formulation comprising a metformin compound.

13. Claims 46,50,54,58,62,66,70,74 and are rejected under 35 U.S.C. 103(a) as being unpatentable over the disclosures of Whitcomb (USPN 6,011,049 hereafter '049).

14. As discussed above the '049 patent discloses a once-a-day metformin formulation for treating diabetes mellitus where the metformin is in concentrations from 300-2000 mg. The claims however recite a 2500 mg dosage form. It is the position of the Examiner that these increased concentrations do not impart patentability on the claims. The patent discloses the general conditions of the claims, namely the large concentration of metformin in a once-a-day dosage form. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *See* In re Aller, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

15. Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various pharmaceutical compositions having various amounts of the active is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges

is not patentable absent a showing of criticality. *See* In re Russell, 439 F.2d 1228 169 USPQ 426 (CCPA 1971).

16. With these things in mind one of ordinary skill in the art would have been motivated to optimize the concentrations of the metformin in order to deliver and improve the method of treating diabetes mellitus. It would have been obvious to follow the disclosures of the '049 patent with an expected result of an optimized once-a-day dosage from capable of treating patients with NIDDM more effectively.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Micah-Paul Young whose telephone number is 571-272-0608. The examiner can normally be reached on M-F 7:00-4:30 every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. 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).

MICHAEL HARTLEY
PRIMARY EXAMINER

Micah-Paul Young
Examiner
Art Unit 1618

MP Young

Notice of References Cited	Application/Control No. 11/225,741	Applicant(s)/Patent Under Reexamination CHEN ET AL.	
	Examiner Micah-Paul Young	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,011,049	01-2000	Whitcomb, Randall Wayne	514/369
	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	
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*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
11/225,741	CHEN ET AL.
Examiner	**Art Unit**
Micah-Paul Young	1618

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	3/30/07
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/225,741	CHEN ET AL.	
Examiner	**Art Unit**	
Micah-Paul Young	1618	

SEARCHED			
Class	Subclass	Date	Examiner
424	464,469, 450,484	12/8/2005	MPY
514	414,415		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
east brs search (uspatfull, uspgpub, derwent , wipo, epo) odp with 11/224,785	12/8/2005	MPY

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

Bib Data Sheet

CONFIRMATION NO. 3874

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/225,741	09/13/2005 RULE	424	1618	300.1005CON

APPLICANTS

Chih-Ming Chen, Davie, FL;

Xiu-Xiu Cheng, Weston, FL;
Steve Jan, Coral Springs, FL;Joseph Chou, Manassas, VA;

** CONTINUING DATA **********
This application is a CON of 10/796,411 03/09/2004
which is a CON of 09/705,630 11/03/2000 PAT 6,866,866

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

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 10/05/2005

Foreign Priority claimed ☐ yes ☑ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials	STATE OR COUNTRY FL	SHEETS DRAWING 8	TOTAL CLAIMS 34	INDEPENDENT CLAIMS 2

ADDRESS
23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK , NY
10018

TITLE
Controlled release metformin compositions

FILING FEE	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time)

091305
01789 U.S. PTO

PTO/SB/05 (05-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. 1.53(b))

Attorney Docket No.	300.1005CON2
First Inventor	Chih-Ming Chen, et al.
Title	CONTROLLED RELEASE METFORMIN COMPOSITIONS
Express Mail Label No.	EV 319 073 952US

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* 43]
   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* 8]
5. **Oath or Declaration** [*Total Sheets* ___]
   a. ☐ Newly executed (original or copy)
   b. ☒ Copy from a prior application (37 CFR 1.63 (d))
   (for a continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named 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)
      i. ☐ Computer Readable Form (CRF)
      ii. ☐ Transfer Request (37 CFR 1.821(e))
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria VA 22313-1450

112963 U.S. PTO
11/225741
091305

ACCOMPANYING APPLICATIONS PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee _____
10. ☐ **37 C.F.R. 3.73(b) Statement** ☐ **Power of Attorney**
    (when there is an assignee)
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of foreign patent documents, publications & other information
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: 10 / 796,411

Prior application information: *Examiner* Micah Paul Young *Art Unit:* 1618

19. CORRESPONDENCE ADDRESS

☒ The address associated with Customer Number 23280 *OR* ☐ Correspondence address below

Name	Davidson, Davidson & Kappel, LLC				
Address	485 Seventh Avenue, 14th Floor				
City	New York	*State*	NY	*Zip Code*	10018
Country	USA	*Telephone*	212-736-1940	*Email address*	DDK@DDKPATENT.COM

Signature		Date	September 13, 2005
Name (Print/Type)	Robert J. Paradiso	*Registration No. (Attorney/Agent)*	41,240

This collection of information is required by 37 CFR 1.53(b). 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 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: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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01789 U.S.PTO
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PTO/SB/17 (12-04v2)
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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	($) 1,700.00

Complete if Known	
Application Number	To be assigned
Filing Date	Herewith
First Named Inventor	Chih-Ming Chen, et al.
Examiner Name	To be assigned
Art Unit	To be assigned
Attorney Docket No.	300.1005CON2

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify) : _____

☒ Deposit Account Deposit Account Number: 50-0552 Deposit Account Name: _____

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

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee($)	Fee($)	Fee($)	Fee($)	Fee($)	Fees Paid ($)
Utility	300	150	500	250	200	100	1,000.00
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($)	Fee Paid ($)
34 -20 or HP=	14	x 50 =	700.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee($)	Fee Paid ($)
2 - 3 or HP=	0	x 0 =	0

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 ($)	Fee Paid ($)
43 - 100 =	0 / 50 =	0 (round **up** to a whole number) x	0	= 0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	0
Other (e.g., late filing surcharge) : _____	0

SUBMITTED BY

Signature	[signature]	Registration No. (Attorney/Agent) 41,240	Telephone 212-736-1940
Name (Print/Type)	Robert J. Paradiso		Date Sept. 13, 2005

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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Calvin Ashby III

Typed or printed name of person signing Certificate

	212-736-1940
Registration Number, if applicable	Telephone Number

EV 319 073 952 US

("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing by Express Mail, or this certificate must identify each submitted paper.

Re.: Docket No.: 300.1005CON2
Applicant(s): Chih-Ming CHEN, et al.
Serial No.: To be assigned
Invention: CONTROLLED RELEASE METFORMIN COMPOSITIONS
Filing Date: Herewith

Enclosed are:
- Continuation Application Transmittal (1 page);
- Fee Transmittal (1 page)
- Specification (43 pages);
- Formal Drawings (8 pages);
- Copy of Executed Declaration and Power of Attorney (2 pages);
- Preliminary Amendment (10 pages);
- Application Data Sheet (2 pages); and
- Check in the amount of $1700.00

This collection of information is required by 37 CFR 1.10. 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 1.8 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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CONTROLLED RELEASE METFORMIN COMPOSITIONS

Background of the Invention

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in United States Patent Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so it can be released through a passageway in the coating membrane or if the active ingredient is insoluble in the permeating fluid, pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in United States Patent Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407 and 4,783,337. United States Patent No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example United States Patent Nos. 4,777,049 and 4,851,229 describe an osmotic dosage form comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have

included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane; i.e., United States Patent Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core; i.e., U.S. Patent Nos. 5,650,170 and 4,892,739.

Although vast amounts of research has been performed on controlled or sustained release compositions and in particular on osmotic dosage forms, very little research has been performed in the area of controlled or sustained release compositions that employ antihyperglycemic drugs.

Metformin is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It is not chemically or pharmacologically related to oral sulfonylureas. Metformin improves glucose tolerance in NIDDM patients by lowering both basal and postprandial plasma glucose. Metformin hydrochloride is currently marketed as GLUCOPHAGE® tablets by Bristol-Myers Squibb Co. Each GLUCOPHAGE® tablet contains 500, 850 or 1000 mg of metformin hydrochloride. There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE®. Dosage of GLUCOPHAGE® is individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose of 2550 mg per day.

Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM. However, being a short acting drug, metformin requires twice-daily (b.i.d.) or three-times-a-day (t.i.d.) dosing. Adverse events associated with metformin use are often gastrointestinal in nature (e.g., anorexia, nausea, vomiting and occasionally diarrhea, etc.). These adverse events may be partially avoided by either reducing the initial and/or maintenance dose or using an extended-release dosage form. Another clear advantage of an extended release dosage form is a reduction in the frequency of administration. All of these findings suggest that an extended-release dosage form of metformin may improve the quality of therapy in patients with NIDDM and the safety profile relative to a conventional dosage form.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride includes the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from

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the dosage form. This research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® metformin HCl product.

It is reported in the 50th Edition of the Physicians' Desk Reference, copyright 1996, p. 753, that food decreases the extent and slightly delays the absorption of metformin delivered by the GLUCOPHAGE® dosage form. This decrease is shown by approximately a 40% lower peak concentration, a 25% lower bioavailability and a 35-minute prolongation of time to peak plasma concentration following administration of a single GLUCOPHAGE® tablet containing 850 mg of metformin HCl with food compared to the similar tablet administered under fasting conditions.

A controlled release metformin dosage form is also described in WO 99/47128. This reference describes a controlled release delivery system for metformin which includes an inner solid particulate phase formed of substantially uniform granules containing metformin and one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials, and an outer continuous phase in which the above granules are embedded and dispersed throughout. The outer continuous phase includes one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials.

Our own WO 99/47125 discloses controlled release metformin formulations providing a Tmax from 8 to 12 hours.

Objects and Summary of the Invention

It is an object of the present invention to provide a controlled or sustained release of an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide a method of treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) on a once-a-day basis with an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide formulations for treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) which provides advantages over

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the state-of-the-art, and which may be administered on a once-a-day basis by itself or together with other antidiabetic agents, and methods thereof.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug wherein the bioavailability of the drug is not decreased by the presence of food.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that does not employ an expanding polymer.

It is also a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that can provide continuous and non-pulsating therapeutic levels of the drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period.

It is an additional object of other embodiments of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels from 5.5 to 7.5 hours after administration under various conditions. Alternatively, the time to peak plasma levels are from 6.0 to 7.0, from 5.5 to 7.0 or from 6.0 to 7.5.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical formulation having a homogeneous core wherein the core component may be made using ordinary tablet compression techniques.

In accordance with the above-mentioned objects and others, the present invention provides a controlled release oral dosage form comprising an antihyperglycemic drug, preferably a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof) that is suitable for providing once-a-day administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration. The dosage form comprises the drug and a membrane. In certain preferred embodiments, the dosage form comprises a tablet.

In preferred embodiments, the controlled release oral dosage form of the present invention is a tablet comprising:

(a) a core comprising:

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(i) the antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

When the drug is metformin or a pharmaceutically acceptable salt thereof and is administered on a once-a-day basis, the daily dose may vary, e.g., from about 500 mg to about 2500 mg. Such daily dose may be contained in one controlled-release dosage form of the invention, or may be contained in more than one such dosage form. For example, a controlled-release metformin dosage form may be formulated to contain about 1000 mg of the drug, and two of said dosage form may be administered together to provide once-a-day metformin therapy. The daily dose of the drug (i.e. metformin or pharmaceutically acceptable salt thereof) may range from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

In certain preferred embodiments, the controlled release solid oral dosage form of the present invention provides a width at 50% of the height of a mean plasma concentration/time curve of the drug (e.g., of metformin) from about 4.5 to about 13 hours, more preferably from about 5.5 to about 10 hours, more preferably from about 6 to about 8 hours.

In certain embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the antihyperglycemic drug which is more than about seven times the mean plasma level of said drug at about 24 hours after administration. In preferred embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the drug which is from about 7 times to about 14 times the plasma level of the drug at about 24 hours after the administration, more preferably from about 8 times to about 12 times the plasma level of the drug at about 24 hours after administration.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release oral dosage form provides a mean

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maximum plasma concentration (C_{max}) of the drug that is about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin, more preferably about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release dosage form provides a mean $AUC_{0\text{-}24hr}$ that is about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; preferably about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; more preferably about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the invention, the administration of the antihyperglycemic drug, e.g., at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from at least 80%, preferably at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of the reference standard (GLUCOPHAGE) twice a day , wherein the daily dose of the reference standard is equal to the once-a day dose of metformin administered in the controlled release oral dosage form of the present invention.

In certain embodiments of the present invention, the controlled release dosage form exhibits the following dissolution profiles of the antihyperglycemic drug (e.g., metformin) when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C: 0-30% of the drug released after 2 hours; 10-45% of the drug released after 4 hours; 30-90% of the drug released after 8 hours; not less than 50% of the drug released after 12 hours; not less than 60% of the drug released after 16 hours; and not less than 70% of the drug released after 20 hours.

In certain preferred embodiments, the controlled release solid oral dosage form exhibits the following dissolution profiles when tested in USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C: 0-25% of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) released after 2 hours; 20-40% of the

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drug released after 4 hours; 45-90% of the drug released after 8 hours; not less than 60% of the drug released after 12 hours; not less than 70% of the drug released after 16 hours; and not less than 80% of the drug released after 20 hours.

With respect to embodiments of the present invention where the antihyperglycemic drug is metformin, it has been found that drugs such as metformin provide substantially linear pharmacokinetics up to a level of about 2 grams per day. Therefore, it is contemplated for purposes of the present invention that a given plasma level (e.g., C_{max}) of metformin per specified dose will be directly proportional to other doses of metformin. Such proportional doses and plasma levels are contemplated to be within the scope of the invention and to be within the scope of the appended claims.

The dosage form of the present invention can provide therapeutic levels of the antihyperglycemic drug for twelve to twenty-four hour periods and does not exhibit a decrease in bioavailability if taken with food. In fact, a slight increase in the bioavailability of the antihyperglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form can be administered once-a-day, ideally with or after a meal, preferably with or after the evening meal, and provides therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 5.5 to 7.5 hours after administration.

The present invention is also directed to a method of lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), said drug being contained in at least one solid oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug may be from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

The controlled release dosage form of the present invention provides a delayed T_{max}, as compared to the T_{max} provided by GLUCOPHAGE. The delayed T_{max} occurs from 5.5 to 7.5

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hours after administration. If the drug (e.g., metformin) is administered at dinner time, the T_{max} would occur during the time when gluconeogenesis is usually at its highest (e.g., around 2 a.m.).

The present invention also includes a method of treating patients with NIDDM comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), contained in at least one oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug may be from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient. In certain embodiments, the method of treatment according to the present invention involves once-per-day metformin monotherapy as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia may not be satisfactorily managed on diet alone. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a sulfonylurea, e.g., when diet and monotherapy with a sulfonylurea alone do not result in adequate glycemic control. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a glitazone, e.g., when diet and monotherapy with a glitazone alone do not result in adequate glycemic control.

The present invention is further directed to a method of controlling the serum glucose concentration in human patients with NIDDM, comprising administering to patients having NIDDM on a once-a-day basis, preferably at dinner time, an effective dose of a biguanide (e.g., metformin) contained in at least one oral controlled release dosage form of the present invention.

The present invention further includes a controlled-release dosage form of a drug comprising a biguanide (e.g., metformin) suitable for once-a-day administration to human patients with NIDDM, the dosage form comprising an effective amount of the drug to control blood glucose levels for up to about 24 hours and an effective amount of a controlled-release carrier to provide controlled release of the drug with a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration and a width at 50% of

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the height of a mean plasma concentration/time curve of the drug from about 6 to about 13 hours. In preferred embodiments, the administration of the controlled-release dosage form occurs at fed state, more preferably at dinner time.

In certain preferred embodiments, the controlled-release dose of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) according to the present invention is provided by one or more of a controlled-release tablet comprising

(a) a core comprising:

(i) the antihyperglycemic drug (e.g., metformin or a pharmaceutically acceptable salt thereof);

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

In certain preferred embodiments, the mean time to maximum plasma concentration of the drug is reached from 6.5 to 7.5 hours after administration at dinner time.

In certain embodiments of the invention when the drug is a biguanide (e.g. metformin or a pharmaceutically acceptable salt thereof), the controlled release dosage form provides upon single administration, a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later, preferably maintaining bioavailability from at least 80% preferably from at least 90% of the immediate release composition.

In certain embodiments of the present invention, the mean fluctuation index of the dosage form is from about 1 to about 4, preferably about 2 to about 3, more preferably about 2.5.

In certain embodiments of the invention which exhibit a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1, preferably about 2:1, more preferably 1.5:1.

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When the drug is metformin or a pharmaceutically acceptable salt thereof, the doses of drug which exhibit the above disclosed mean fluctuation indexes can be any effective dose administered to a patient with NIDDM for the reduction of serum glucose levels. For example, the dose can from about 500mg to about 2500mg, from about 1000mg to about 2000 mg or from about 850mg to about 1700mg metformin or pharmaceutically acceptable salt thereof.

The drugs which may used in conjunction with the present invention include those drugs which are useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), including but not limited to biguinides such as metformin or buformin or pharmaceutically acceptable salts thereof. When the drug used in the present invention is metformin, it is preferred that the metformin be present in a salt form, preferably as metformin hydrochloride.

The term "metformin" as it is used herein means metformin base or any pharmaceutically acceptable salt e.g., metformin hydrochloride.

The term "dosage form" as it is used herein means at least one unit dosage form of the present invention (e.g. the daily dose of the antihyperglycemic agent can be contained in 2 unit dosage forms of the present invention for single once-a-day administration).

The term "morning" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered early in the day after the patient has awakened from overnight sleep, generally between about 6 a.m. and 11 a.m. (regardless of whether breakfast is eaten at that time, unless so specified herein).

The term "dinnertime" or "at dinner" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered at a time when dinner is normally eaten (regardless of whether a meal is actually eaten at that time, unless so specified herein), generally between about 4 p.m. and 8 p.m.

The term "bedtime" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered before the patient goes to bed in the evening, generally between about 8 p.m. and 12 p.m.

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The term "therapeutically effective reduction" when used herein is meant to signify that blood glucose levels are reduced by approximately the same amount as an immediate release reference standard (e.g., GLUCOPHAGE®) or more, when the controlled release dosage form is orally administered to a human patient on a once-a-day basis.

The term "sustained release" and "controlled release" are used interchangeably in this application and are defined for purposes of the present invention as the release of the drug from the dosage form at such a rate that when a once-a-day dose of the drug is administered in the sustained release or controlled-release form, blood (e.g., plasma) concentrations (levels) of the drug are maintained within the therapeutic range but below toxic levels over a period of time from about 12 to about 24 hours. When the drug used in the present invention is metformin (preferably metformin hydrochloride) the controlled release solid oral dosage form containing such drug is also referred to as "Metformin XT."

The term "C_{max}" is the highest plasma concentration of the drug attained within the dosing interval, i.e., about 24 hours.

The term "C_{min} " is the minimum plasma concentration of the drug attained within the dosing interval, i.e. about 24 hours.

The term "C_{avg}" as used herein, means the plasma concentration of the drug within the dosing interval, i.e. about 24-hours, and is calculated as AUC/dosing interval.

The term "T_{max}" is the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours).

The term "AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete 24-hour interval.

The term "steady state" means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose of the formulation.

The term "single dose" means that the human patient has received a single dose of the drug formulation and the drug plasma concentration has not achieved steady state.

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The term "multiple dose" means that the human patient has received at least two doses of the drug formulation in accordance with the dosing interval for that formulation (e.g., on a once-a-day basis). Patients who have received multiple doses of the controlled release formulations of the invention may or may not have attained steady state drug plasma levels, as the term multiple dose is defined herein.

The term "a patient" means that the discussion (or claim) is directed to the pharmacokinetic parameters of an individual patient and/or the mean pharmacokinetic values obtained from a population of patients, unless further specified.

The term "mean", when preceding a pharmacokinetic value (e.g. mean T_{max}) represents the arithmetic mean value of the pharmacokinetic value taken from a population of patients unless otherwise specified (e.g. geometric mean)..

The term "Degree of Fluctuation" is expressed as $(C_{max} - C_{min})/C_{avg}$.

Brief Description of the Drawings

FIG. 1 is a graph showing the relative bioavailability of the metformin XT formulation of Example 2 to GLUCOPHAGE® for Clinical Study 2.

FIG. 2 is a graph showing the relative bioavailability of the metformin XT formulation of Example 1 (500 mg) to GLUCOPHAGE® for Clinical Study 3.

FIG. 3 is a graph showing the difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day 1 and Day 14 dosing following oral administration of the metformin XT formulation of Example 1, 4 x 500 mg q.d. for 14 days for Clinical Study 4.

FIG. 4 is a graph showing the mean plasma profiles and values of pharmacokinetic parameters of the metformin XT formulation of Example 3 for Clinical Study 5.

FIG. 5 is a graph showing the mean plasma glucose concentration-time profiles after 4 weeks of treatment with the metformin XT formulation of Example 3 and GLUCOPHAGE® for Clinical Study 5.

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FIG. 6 is a graph showing the dissolution profile of a 500 mg controlled release metformin formulation of Example 1 of the present invention.

FIG. 7 is a graph showing the dissolution profile of a 850 mg controlled release metformin formulation of Example 2 of the present invention.

FIG. 8 is a graph showing the dissolution profile of a 1000 mg controlled release metformin formulation of Example 3 of the present invention.

Detailed Description of the Invention

The term antihyperglycemic drugs as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Preferably, the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride.

It has surprisingly been found that when biguanides such as metformin are administered orally in a controlled release dosage form suitable for once-a-day dosing in the "fed" state, preferably at dinner, the bioavailability is improved as compared to the administration of the controlled release dosage form in the "fasted" state. This is in contrast to GLUCOPHAGE®, which exhibits opposite characteristics. In accordance with the methods and dosage forms of the present invention, it has been determined that the patients suffering from NIDDM achieve improved results (e.g., lowered blood glucose levels) than GLUCOPHAGE® administered according to accepted protocols, e.g., on a twice-a-day basis.

The methods and dosage forms of the invention provide the further advantage in that when dosed at dinnertime, the controlled release formulations of the invention provide a T_{max} (from 5.5 to 7.5 hours) after oral administration (which T_{max} is delayed relative to the reference standard, GLUCOPHAGE®), such that the level of drug is greatest at the time when human patients are manufacturing glucose at highest levels. Gluconeogenesis is well known to those skilled in the art to be greatest at night. Thus, in accordance with the invention, the T_{max} of the drug occurs for example between 11:30 p.m. and 1:30a.m., based on a dose administered at 6:00 p.m. Likewise, such administration of the dosage form provides lower drug levels during the day

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(e.g. the afternoon) when gluconeogenesis is lower than at night. Also, the invention preferably provides the added benefit of lowering insulin levels. Insulin is considered a risk factor in NIDDM, in and of itself, for cardiovascular disease.

In comparison to a twice-daily dose of the reference standard (GLUCOPHAGE®), the plasma levels of metformin are preferably lower in the afternoon. This is an advantage particularly in patients who are under concomitant therapy with one or more additional antidiabetic agents, such as for example, a sulfonylurea. It is known in the art that to date approximately 60% of patients being treated with metformin are also being treated with at least one additional antidiabetic agent (such as a sulfonylurea). Sulfonylureas can possibly cause hypoglycemia, whereas metformin cannot, so there is a benefit to having lower metformin levels in the blood during the afternoon due to the potential for the patient to have hypoglycemia.

Accordingly, the present invention also includes a method of treating human patients with NIDDM comprising administering on a once-a-day basis a therapeutically effective dose of metformin in a controlled-release oral dosage form ("Metformin XT"), in combination with administering an effective amount of a sulfonylurea. In preferred embodiments, metformin is provided by a controlled release dosage form comprising metformin or a pharmaceutically acceptable salt thereof, the dosage form being useful for providing a once-a-day oral administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.5 hours after administration.

In certain embodiments, the combination therapy may be provided as follows. If patients do not respond to four weeks of the maximum dose of Metformin XT (2500 mg/ day) monotherapy, a sulfonylurea may be gradually added while maintaining the maximum dose of Metformin XT, even if prior primary or secondary failure to a sulfonylurea has occurred. Examples of the sulfonylurea include glyburide (glibenclamid), chloropropamide, tolbutamide, glipizide, acetohexamide and tolazamide. Although Metformin XT is preferably administered on once-a-day basis, the sulfonylurea may be administered in a different dosage form and at a different frequency.

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With concomitant Metformin XT and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

In certain embodiments, the foregoing objectives are met by a controlled release dosage form comprising:

(a) a core comprising:

(i) an antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

The binding agent may be any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose, polymethacrylate, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent comprises approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core.

The core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-big (B-aminoethyl ether -N,N,N,N-tetraacetic acid (EGTA). The core comprises approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

In this embodiment, the core which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption

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enhancer is preferably formed by wet granulating the core ingredients and compressing the granules with the addition of a lubricant into a tablet on a rotary press. The core may also be formed by dry granulating the core ingredients and compressing the granules with the addition of a lubricant into tablets or by direct compression.

Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

The homogeneous core is coated with a membrane, preferably a polymeric membrane to form the controlled release tablet of the invention. The membrane can be a semipermeable membrane by being permeable to the passage of external fluid such as water and biological fluids and being impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in United States Patent Nos. 3,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference. The most preferred membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increases the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux enhancing agent can be a water soluble material or an enteric material. Some examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxyprophy methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

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The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts or a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug which is selected as the flux enhancer.

The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the membrane to form paths in the membrane for the fluid to enter the core and dissolve the active ingredient.

In alternate embodiments, the membrane may also be formed with commonly known excipients such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, and the like. Depending on the particular plasticizer, amounts of from 0 to about 25%, and preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. A detailed description of the passageway can be found in United States Patent Nos. such as 3,845,770, 3,916,899, 4,034,758, 4,063,064, 4,077,407, 4,088,864, 4,783,337 and 5,071,607 (the disclosures of which are hereby incorporated by reference).

In certain embodiments, the passageway is formed by laser drilling. In other embodiments, the passageway is formed by making an indentation onto the core prior to the membrane coating to form a weakened area of the membrane at the point of the indentation. In

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preferred embodiments of the invention, the dosage form contains two passageways in order provide the desired pharmacokinetic parameters of the formulation.

Generally, the membrane coating around the core will comprise from about 1% to about 7%, preferably about 1.5% to about 3%, based on the total weight of the core and coating.

The term "membrane" means a membrane that is permeable to both aqueous solutions or bodily fluids and to the active drug or pharmaceutical ingredient (e.g. the formulations of Examples 1-3). Thus, the membrane is porous to drug and, in a preferred embodiment, drug is released through the hole or passageway and through the porous membrane in solution or in vivo. The term "membrane" also generically encompasses the term "semipermeable membrane" as heretofore defined.

In an alternative embodiment, the dosage form of the present invention may also comprise an effective amount of the antihyperglycemic drug that is available for immediate release. The effective amount of antihyperglycemic drug for immediate release may be coated onto the membrane of the dosage form or it may be incorporated into the membrane.

In certain preferred embodiments of the invention where the dosage form is prepared in accordance with the above, the dosage form will have the following composition:

INGREDIENT	Preferred	Most Preferred
CORE:		
Drug	50-98%	75-95%
Binder	0-40%	3-15%
Absorption Enhancer	0-20%	2-10%
COATING:		
Membrane Polymer	50-99%	75-95%
Flux Enhancer	0-40%	2-20%
Plasticizer	0-25% or 0-30%	2-15%

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The dosage forms prepared according to certain embodiments of the present invention preferably exhibit the following dissolution profile when tested in a USP type 2 apparatus at 75 rpms in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:

Time (Hours)	Preferred	Most Preferred
2	0-30%	0-15% or 0-25%
4	10-45%	20-40%
8	30-90%	45-90%
12	NTL 50%	NTL 60%
16	NTL 60%	NTL 70%
20	NTL 70%	NTL 80%

NTL = Not less than

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants, etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention.

Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients. Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art. In either case, the controlled release dosage form may optionally include a

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controlled release carrier which is incorporated into a matrix along with the drug, or which is applied as a controlled release coating.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates") and/or particles. An amount of the multiparticulates which is effective to provide the desired dose of drug over time may be placed in a capsule or may be incorporated in any other suitable oral form.

In certain preferred embodiments, the tablet core or multiparticulates containing the drug are coated with a hydrophobic material selected from (i) an alkylcellulose and (ii) a polymeric glycol. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like as previously disclosed.

Description of Certain Preferred Embodiments

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

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Example 1

A controlled release tablet containing 500 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	500.0
Povidone[3], USP	36.0
Sodium Lauryl Sulfate	25.8
Magnesium Stearate	2.8

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

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(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	21.5
Triacetin	1.3
PEG 400	2.5

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

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Example 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	850.0
Povidone[3], USP	61.1
Sodium Lauryl Sulfate	43.9
Magnesium Stearate	4.8

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

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(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	24.0
Triacetin	1.4
PEG 400	2.8

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

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Example 3

A controlled release tablet containing 1000 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tablet)
Metformin HCl	1000.0
Povidone[3], USP	71.9
Sodium Lauryl Sulfate	51.7
Magnesium Stearate	5.6

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with a screen equivalent to 18 mesh.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with ½" round standard concave punches.

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(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7003), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The core tablet is coated with the sealing solution until the tablet is coated with 23.0 mg/tablet of the Opadry material.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	19.0
Triacetin	1.1
PEG 400	2.2

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

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(e) **Color Coating (optional)**

Subsequent to the sustained release coating, the laser drilled tablet is coated with a color coating using Opadry White (24 mg/tablet) and waxed with Candelilla wax powder (0.4 mg/tablet).

Clinical Studies

Study 1

In study 1, a total of twelve (12) healthy subjects (six males, six females) were randomized to receive either a single oral dose of metformin XT, 850mg, prepared in accordance with Example 2 or b.i.d. doses of GLUCOPHAGE in assigned study periods which consisted of one of the following groups: Group A - metformin XT (2 x 850 mg tablets) taken at approximately 8:00 a.m., immediately following breakfast, Group B - metformin XT (2 x 850 mg tablets) taken at approximately 6:00 p.m., immediately following dinner; and Group C - GLUCOPHAGE (1 x 850 mg tablet) taken at approximately 8:00 a.m., immediately following breakfast, and at approximately 6:00 p.m., immediately following dinner. Each drug administration was separated by a washout period of seven days. In this study, one male subject was removed from the study prior to Period II due to non-treatment-related mononucleosis. Thus, 11 (five males and six females) subjects completed the study.

For metformin XT, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hour(s) after dosing. For GLUCOPHAGE, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, and 24 hour(s) after the first dose in the morning. Plasma concentrations of metformin were determined using a validated HPLC method. The lower quantitation limit of this method is 10 ng/ml. Mean plasma concentration-time profiles are shown in Fig. 1 and mean values of pharmacokinetic parameters of metformin obtained from this study are presented in Table 1.

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Table 1

Mean (±SD, n = 11) values of pharmacokinetic parameters of metformin (Example 2) in 11 healthy subjects (metformin XT, 2 x 850 mg q.d. or GLUCOPHAGE, 1 x 850 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	**$AUC_{0-\infty}$ (ng-hr/ml)**	**C_{max} (ng/ml)**	**T_{max} (hr.)**	**T_{lag} (hr)**	**$t_{1/2}$ (hr)**	$AUC_{0-\infty}$	C_{max}
Metformin XT after breakfast	18156 (4183)	2045 (567)	6 (2)	0.18 (0.40)	4.4 (0.7)	1.00	1.36
Metformin XT after dinner	18277 (2961)	1929 (333)	7 (2)	0.09 (0.30)	3.6 (0.8)	1.02	1.32
GLUCOPHAGE	18050 (3502)	1457 (217)	5 (3)	0 (0)	3.5 (0.9)	–	–

*Ratio = Metformin XT/GLUCOPHAGE

As shown in Figure 1 and Table 1, when metformin XT was administered immediately after either breakfast or dinner, the relative bioavailability of metformin XT formulation to GLUCOPHAGE is approximately 100%.

The results of study 1 were used to calculate the approximate degree of fluctuation (C_{max} - C_{min}/C_{avg}) of the formulations.

The C_{max} was directly obtained from the study (see Table 1). The C_{avg} was obtained by dividing the AUC value by the dosing interval, i.e. 24 hours. The value for C_{min} was extrapolated from Figure 1.

The results are set forth in Table 2 below:

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Table 2

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 2 x 850 mg q.d. and GLUCOPHAGE, 850 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT after breakfast	18156 (4183)	2045 (567)	143	756	2..51
Metformin XT after dinner	18277 (2961)	1929 (333)	107	761	2.39
GLUCOPHAGE	18050 (3502)	1457 (217)	214 (at 24 hours)	752	1.65
			393 (between doses)	752	1.41

As shown in Figure 1 and Table 2, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than a substantially equal dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 2

The study design of Study 2 is the same as Study 1 except for the formulation and the dose (4 x 500 mg q.d., total dose 2000mg, for metformin XT prepared according to Example 1 and 2 x 500 mg b.i.d., total dose 2000mg, for GLUCOPHAGE in the second study). In this study, 12 healthy volunteers (five males and seven females) were randomized to receive treatments and completed the study. Mean plasma concentration-time profiles and mean values

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of pharmacokinetic parameters of metformin obtained from this study are presented in Figure 2 and Table 3.

As shown in Figure 2 and Table 3, when the metformin XT formulation (500 mg) was administered immediately after dinner, the relative bioavailability of this formulation to GLUCOPHAGE is approximately 100%, while the mean C_{max} value is about the same. The relative bioavailability of metformin XT, however, is approximately 80% when administered immediately after breakfast. A prolonged profile, together with later T_{max} and similar C_{max} of metformin following administration of metformin XT immediately after dinner compared to GLUCOPHAGE indicated that metformin was released *in vivo* in a sustained fashion (Figure 2).

Table 3

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin of Example 1 in 12 healthy subjects (metformin XT, 4 x 500 mg q.d. or GLUCOPHAGE, 2 x 500 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	**$AUC_{0-\infty}$ (ng-hr/ml)**	**C_{max} (ng/ml)**	**T_{max} (hr)**	**T_{lag} (hr)**	**$t_{1/2}$ (hr)**	$AUC_{0-\infty}$	C_{max}
Metformin XT after breakfast	17322 (4984)	2127 (545)	5 (1)	0 (0)	6.1 (1.8)	0.80	1.15
Metformin XT after dinner	20335 (4360)	2053 (447)	7 (2)	0.08 (0.29)	3.9 (0.6)	0.96	1.12
GLUCOPHAGE	21181 (4486)	1815 (302)	4 (3)	0 (0)	3.6 (0.8)	--	–

*Ratio = Metformin XT/GLUCOPHAGE

The results of study 2 were used to calculate the approximate degree of fluctuation of the formulations in accordance with the calculations used in study 1 (using Figure 2 to obtain the extrapolated value for C_{min}).

The results are set forth in Table 4 below:

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Table 4

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 4 x 500 mg q.d. and GLUCOPHAGE, 2 x 500 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT after breakfast	17322 (4984)	2127 (545)	143	721	2.9
Metformin XT after dinner	20335 (4360)	2053 (447)	143	847	2.25
GLUCOPHAGE	21181 (4486)	1815 (302)	214 (at 24 hours)	882	1.8
			357 (between doses)	882	1.65

As shown in Figure 2 and Table 4, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than an equivalent dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 3

In Study 3, a multiple-dose, open-label, one-period study was conducted to evaluate the short-term tolerability and steady-state pharmacokinetics of the 500 mg metformin XT formulation used in Study 2. In this study, eight healthy volunteers (four males and four females) were randomized to receive 2000 mg of metformin XT (4 x 500 mg tablets) at approximately 6:00 p.m., immediately following dinner, for 14 days.

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Blood samples were obtained from each subject at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hour(s) following the first dose on Day 1 and at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 38 and 48 hour(s) following the last dose on Day 14. Blood samples were also drawn from each subject immediately prior to dosing on Days 10-13. Urine samples were collected from each subject at the following time intervals: six hours prior to the first dose; 0-6, 6-12 and 12-24 hours after the first dose; and 0-6, 6-12, 12-24 and 24-48 hours after the last dose.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in Table 5 below:

Table 5

Mean Pharmacokinetic Parameters (Example 1)

Day 1

	C_{max}	T_{max}	$AUC_{0\text{-}24hr\ (ng.hr/ml)}$
Mean	2435	6.9	22590
SD	630	1.9	3626

Day 14

	C_{max}	T_{max}	$AUC_{0\text{-}24hr\ (ng.hr/ml)}$
Mean	2288	6.9	24136
SD	736	2.5	7996

Following oral administration of metformin XT, 4 x 500 mg q.d., for 14 days, there was little or no difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day 1 and Day 14 dosing (Figure 3). On average, trough plasma concentrations of metformin were nearly constant, ranging from 188.8 to 205.1 ng/ml on Days 10-14, indicating that the steady state of metformin was attained rapidly. The mean

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accumulation ratio was 1.01, indicating that the once-daily dose regimen of metformin XT results in no accumulation.

Following oral administration of a single dose (4 x 500 mg) of metformin XT, approximately 31% of the dose was excreted in the urine within the first 24 hours. On average, the renal clearance of metformin was 366 ml/min. A slightly higher renal clearance (454 ml/min) was found after multiple-dose administration of 4 x 500 mg q.d. of metformin XT.

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence and anorexia) are the most common adverse reactions to GLUCOPHAGE. In controlled trials, GLUCOPHAGE was started at low, nontherapeutic doses and gradually titrated to higher doses. In spite of this gradual titration, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. In contrast, in the multiple-dose study, metformin XT begun at a therapeutic initial dose of 2000 mg once daily with dinner was well tolerated by all healthy volunteers. Diarrhea and nausea were the most common gastrointestinal reactions probably or possibly related to metformin XT. These reactions, however, were either mild or moderate. This suggests that it may be possible to initiate metformin XT treatment with effective doses rather than using the slow titration from non-therapeutic doses required for GLUCOPHAGE.

Study 4

Study 4 was a study designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of metformin XT compared to GLUCOPHAGE after multiple-dose treatment in patients with NIDDM. Metformin XT tablets prepared according to Example 3 were used in this study. This study had a single-center, randomized, two-way crossover design. A total of 24 NIDDM patients who were on a stable dose of GLUCOPHAGE, between 1000 and 2550 mg/day, for at least 12 weeks were selected for the study. A Pretreatment Period of at least 3 weeks preceded randomization to study treatment. At the start of the Pretreatment Period, all patients stopped taking any other hypoglycemic agents besides GLUCOPHAGE, and the GLUCOPHAGE dose was adjusted to 1000 mg b.i.d. (with breakfast and with dinner).

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Following the pretreatment period, patients began Treatment Period I, which lasted 4 weeks. During Period I, a total of 12 patients were randomized to receive two 1000-mg metformin XT tablets q.d. (immediately after dinner), at approximately 6:00 p.m., and 12 were randomized to receive one 1000-mg GLUCOPHAGE tablet b.i.d. (immediately after breakfast and immediately after dinner). Immediately following Period I, each patient was switched to the alternate medication for 4 weeks in Period II. There was no washout between treatment periods.

Plasma metformin concentrations were determined over a 24-hour period at the end of Treatment Periods I and II as follows: immediately prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 15, 16, 17, 18, 19, 20, 22, and 24 hours after the evening dose. One subject withdrew from the study for personal reasons after two weeks of treatment in Treatment Period I, thus pharmacokinetic data were obtained from 23 patients.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in Figure 4 and Table 6. As shown in Figure 4 and Table 6, when metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state is close to 100%. Although the dose of metformin XT was twice as large as the dose of GLUCOPHAGE at dinner, the mean C_{max} value was only 32% higher.

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Table 6

Mean (± SD) values of pharmacokinetic parameters of metformin of Example 3 in 23 NIDDM patients (metformin XT, 2 x 1000 mg q.d. with dinner or GLUCOPHAGE, 1 x 1000 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	AUC_{0-24hr} (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	T_{lag} (hr)	$t_{½}$ (hr)	AUC_{0-24hr}	C_{max}
Metformin XT after dinner	26818 (7052)	2849 (797)	6 (2)	0 (0)	5.4	0.96	1.32
GLUCOPHAGE	27367 (5759)	2131 (489)	14 (6)	0 (0)	4.4	--	--

* Ratio = Metformin XT/GLUCOPHAGE

When the metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state was close to 100%. However, when metformin XT was administered immediately after breakfast, the corresponding relative bioavailability of metformin XT was approximately 80%. The safety profile of metformin XT, 2000 mg given once daily either after dinner or after breakfast was comparable to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy profile of metformin XT, 2000 mg given once daily after dinner was similar to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy of metformin XT, 2000 mg given once daily after breakfast, however, appeared to be comparable to or slightly less than that of GLUCOPHAGE given b.i.d.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

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WHAT IS CLAIMED IS:

1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of at least one suitable antihyperglycemic drug or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form being suitable for providing once-a-day oral administration of the agent or pharmaceutically acceptable salt thereof, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the agent from 5.5 to 7.5 hours after the administration.

2. The controlled release dosage form of claim 1 wherein said at least one antihyperglycemic drug is a biguanide.

3. The controlled release dosage form of claim 2 wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

4. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from 6.0 to 7.0 hours after the administration of the dose.

5. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.0 hours after the administration of the dose, when the dose is administered at dinner time.

6. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from about 6.0 to 7.5 hours after the administration of the dose, when the dose is administered at breakfast.

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7. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:
0-30% of the drug is released after 2 hours;
10-45% of the drug is released after 4 hours;
30-90% of drug is released after 8 hours;
not less than 50% of the drug is released after 12 hours;
not less than 60% of the drug is released after 16 hours; and
not less than 70% of the drug is released after 20 hours.

8. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:
0-25% of the drug is released after 2 hours;
20-40% of the drug is released after 4 hours;
45-90% of the drug is released after 8 hours;
not less than 60% of the drug is released after 12 hours;
not less than 70% of the drug is released after 16 hours; and
not less than 80% of the drug is released after 20 hours.

9. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 4.5 to about 13 hours.

10. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 5.5 to about 10 hours.

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11. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

12. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

13. The controlled release oral dosage form of claim 3 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

14. The controlled release oral dosage form of claim 3 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

15. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ of at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

17. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release

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reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

18. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

19. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

20. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

21. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

22. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

23. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

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24. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 6, based on administration of a 2000 mg once-a-day dose of metformin at breakfast.

25. The controlled release oral dosage form of claim 3 which provides a mean plasma glucose concentration-time profiles substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

26. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

27. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.0 hours after administration at dinner time.

28. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.5 hours after administration at breakfast.

29. The controlled release dosage form of claim 1, wherein the metformin is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:

(i) the metformin or a pharmaceutically acceptable salt;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

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30. The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

31. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising at least one biguanide or pharmaceutically acceptable salt thereof and a controlled release carrier wherein a single administration of said dosage form provides a higher mean fluctuation index in the plasma than a substantially equal dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

32. The controlled release oral dosage form of claim 31 wherein the mean fluctuation index of the dosage form is from about 1 to about 4.

33. The controlled release oral dosage form of claim 32 wherein the mean fluctuation index of the dosage form is from about 2 to about 3.

34. The controlled release oral dosage form of claim 33 wherein the mean fluctuation index of the dosage form is about 2.5.

35. The controlled release oral dosage form of claim 31 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1.

36. The controlled release oral dosage form of claim 35 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 2:1.

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37. The controlled release oral dosage form of claim 36 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 1.5:1.

38. The controlled release oral dosage form of claim 31 wherein said dosage form comprises metformin or a pharmaceutically acceptable salt thereof.

39. The controlled release oral dosage form of claim 31 wherein said dosage form maintains bioavailability from at least about 80% of the immediate release composition.

40. The controlled release oral dosage form of claim 31 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 500mg to about 2500 mg metformin or pharmaceutically acceptable salt thereof.

41. The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 1000mg to about 2000 mg metformin or pharmaceutically acceptable salt thereof.

42. The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 850mg to about 1700mg metformin or pharmaceutically acceptable salt thereof.

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ABSTRACT

A composition for treating patients having non-insulin-dependent diabetes mellitus (NIDDM) by administering a controlled release oral solid dosage form containing preferably a biguanide drug such as metformin, on a once-a-day basis. The dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 5.5 to 7.5 hours after oral administration on a once-a-day basis to human patients. Preferably, the dose of drug is administered at dinnertime to a patient in the fed state.

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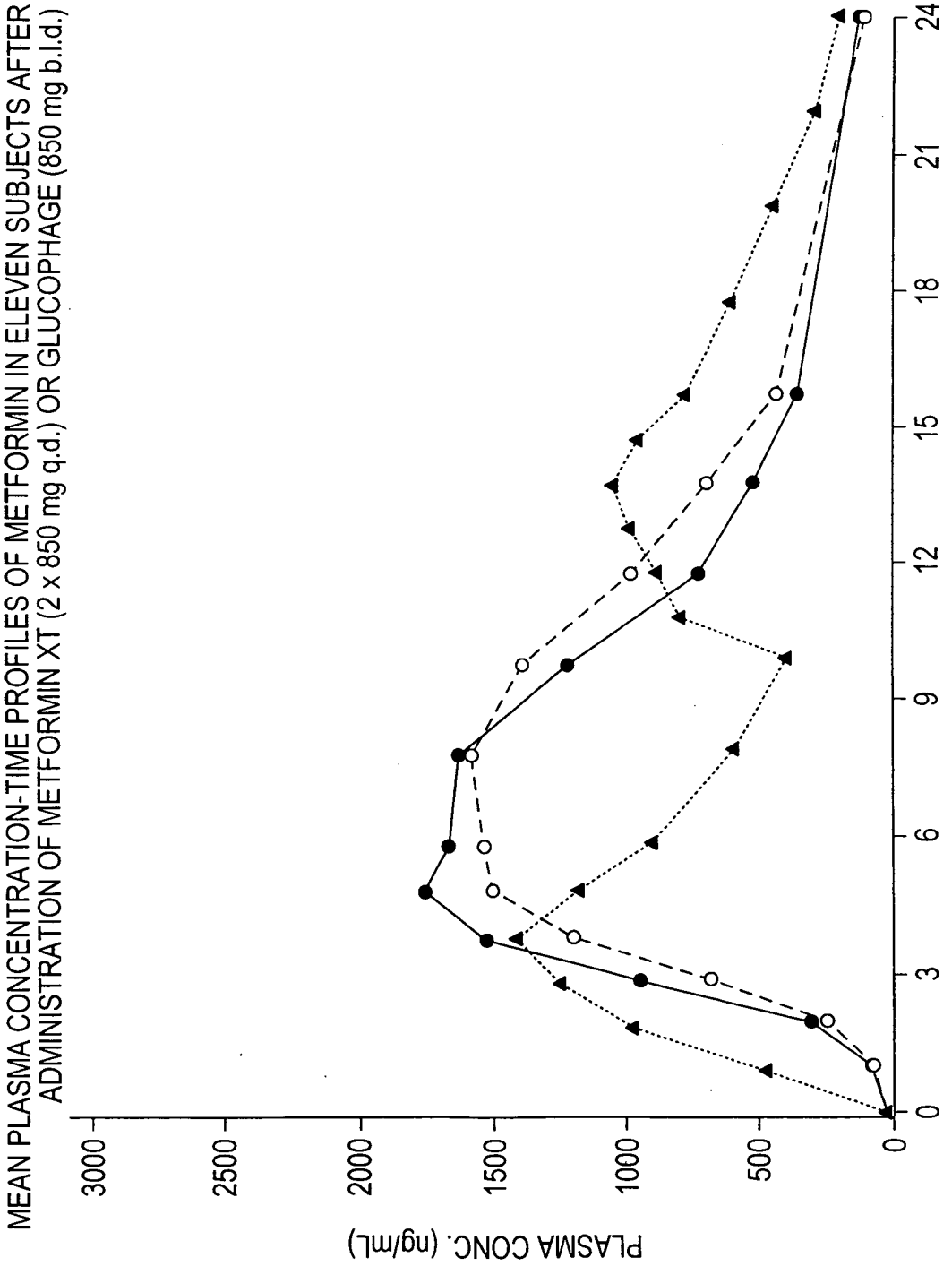

FIG. 1

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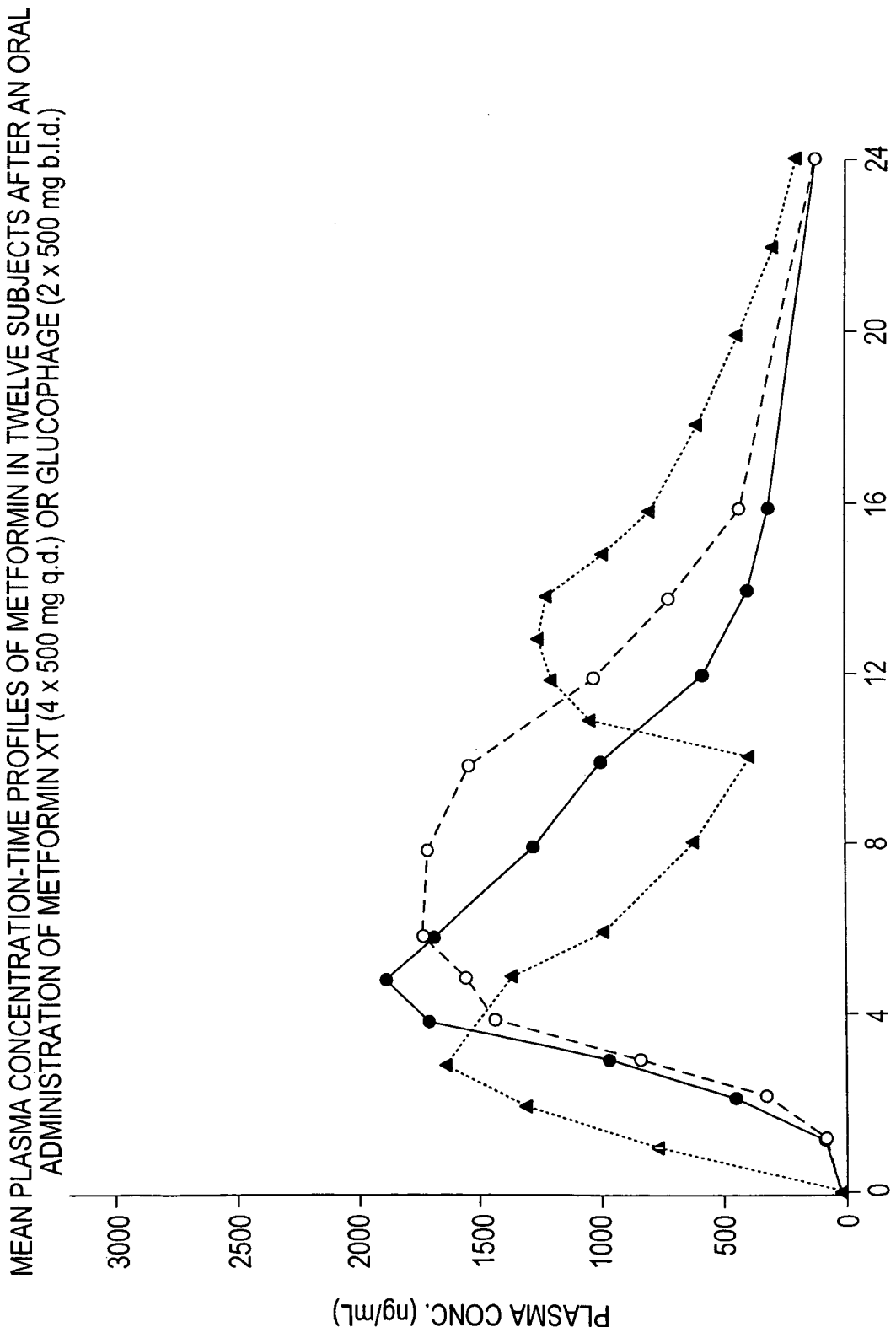
MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN TWELVE SUBJECTS AFTER AN ORAL ADMINISTRATION OF METFORMIN XT (4 x 500 mg q.d.) OR GLUCOPHAGE (2 x 500 mg b.i.d.)
PLASMA CONC. (ng/mL)
3000
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
TIME (hr)
METFORMIN XT q.d. AFTER BREAK
METFORMIN XT q.d. AFTER DINNER
GLUCOPHAGE b.i.d.

FIG. 2

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN EIGHT HEALTHY SUBJECTS AFTER MULTIPLE ORAL DOSES OF METFORMIN XT (4 x 500 mg q.d.)

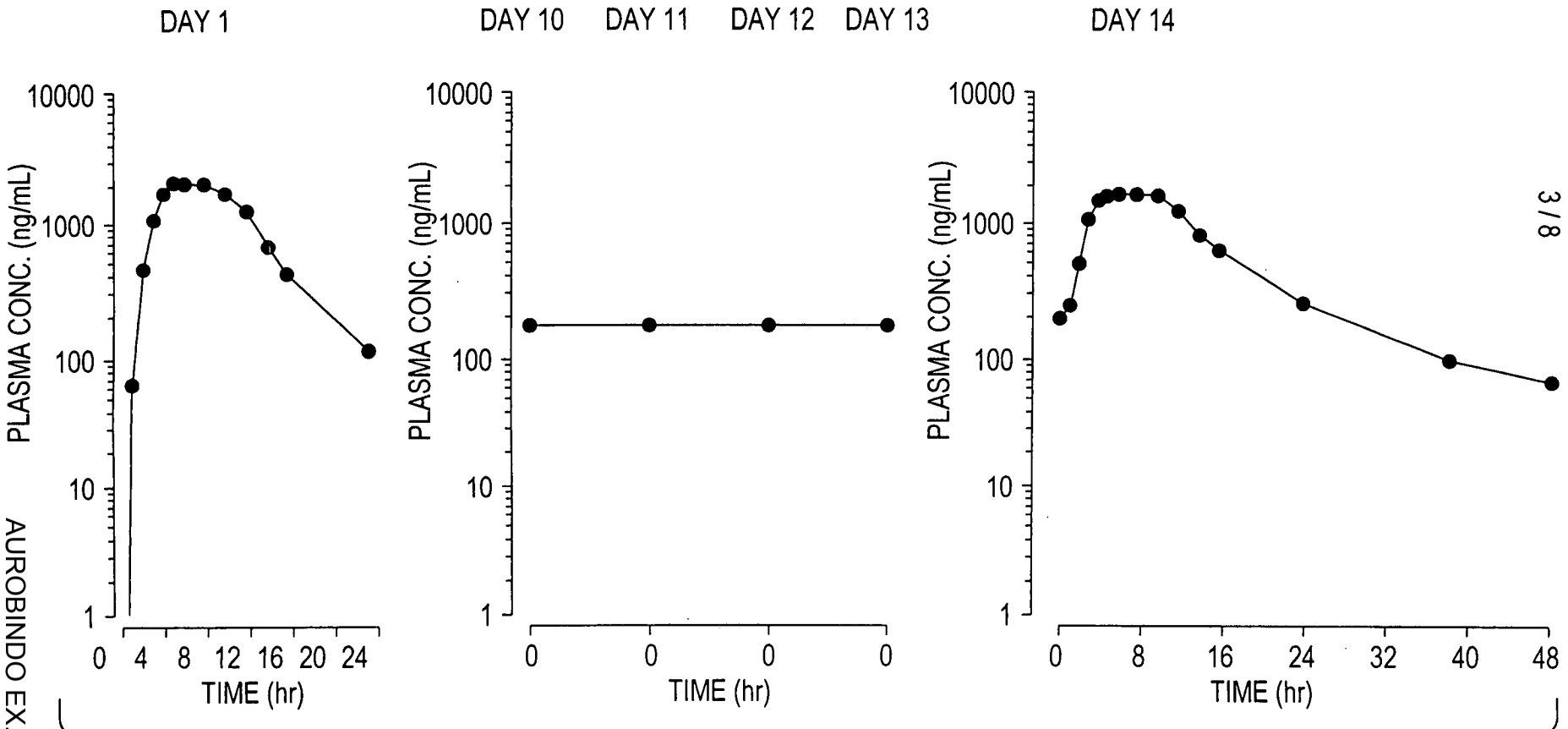

FIG. 3

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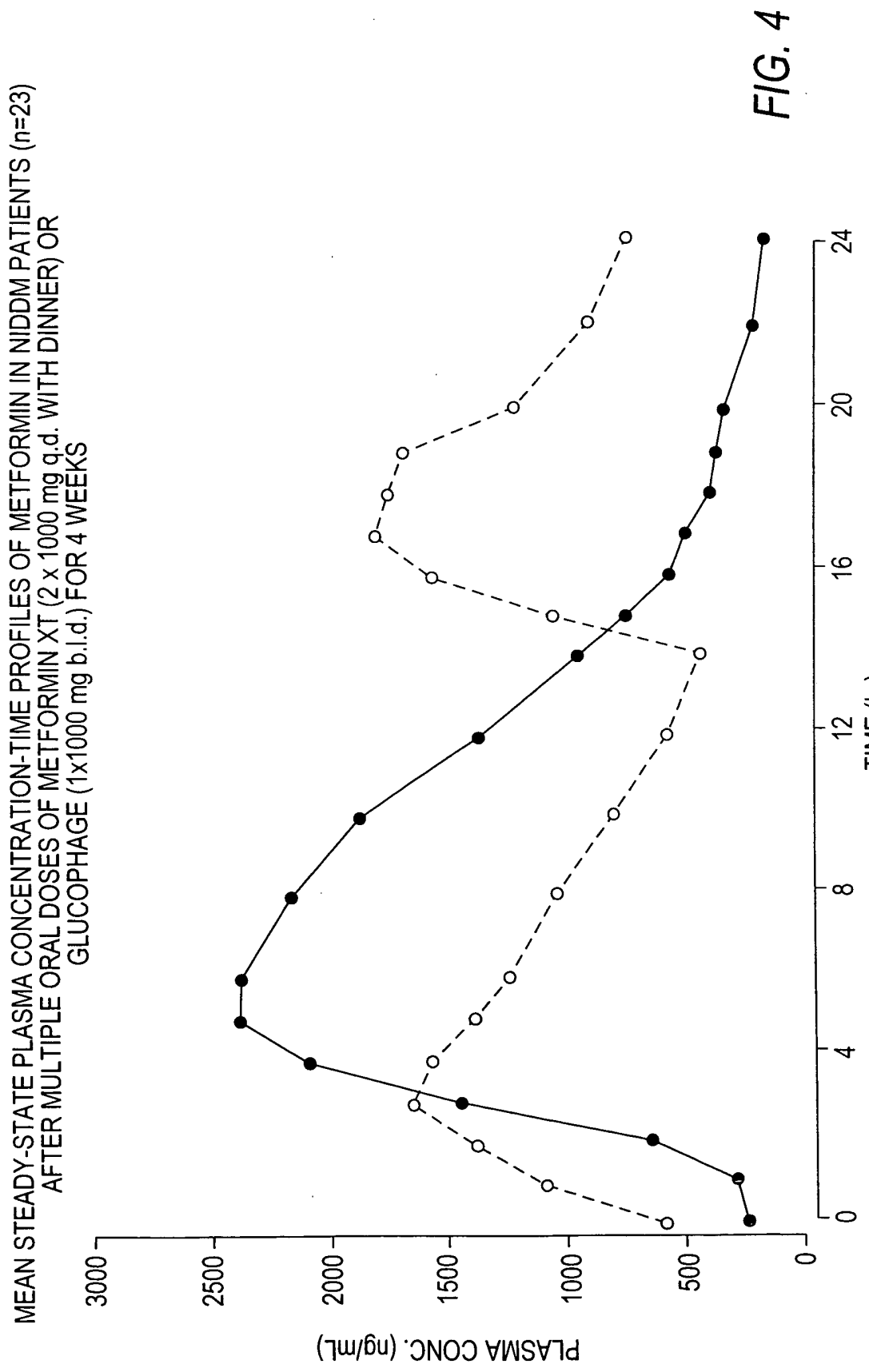

FIG. 4

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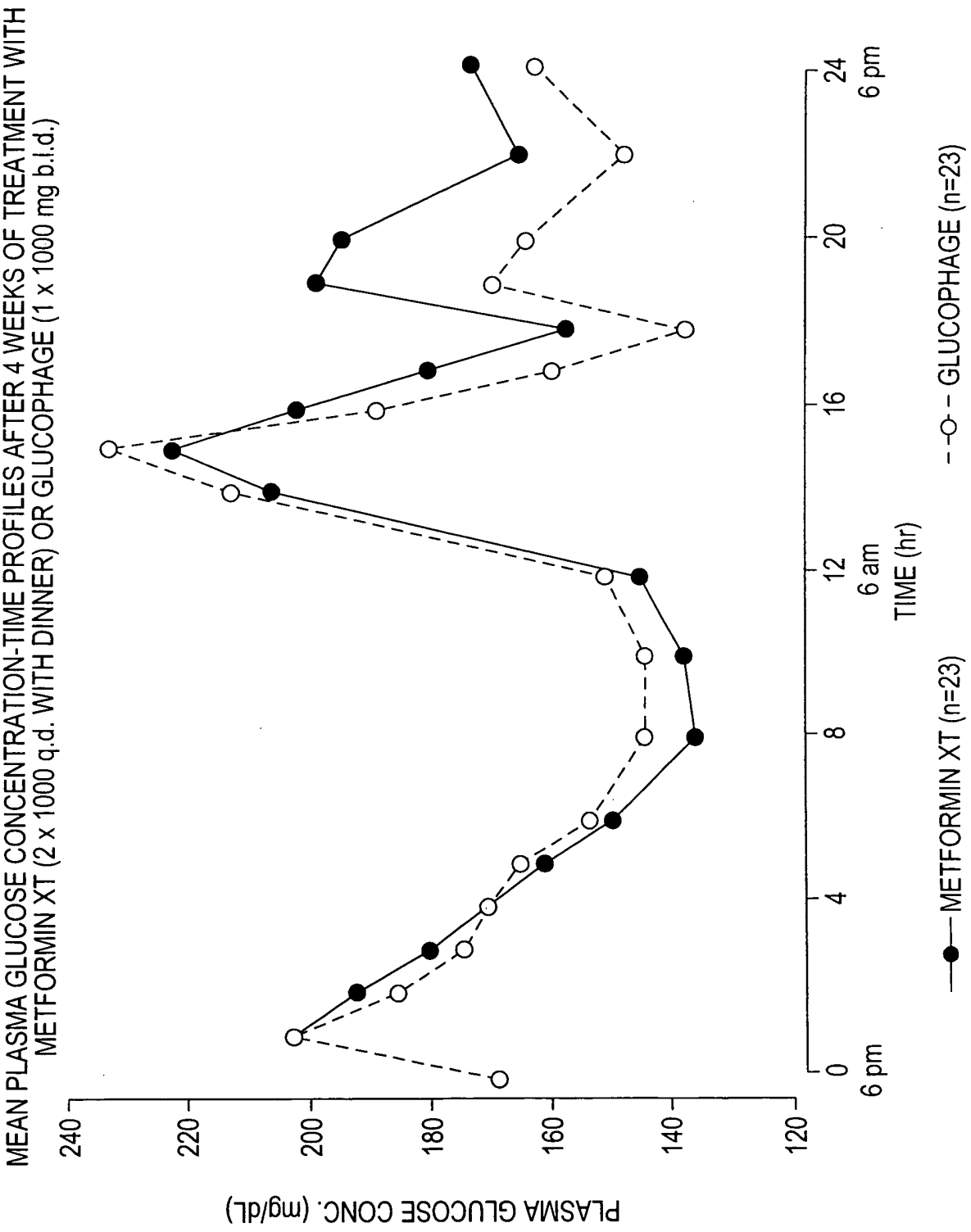
MEAN PLASMA GLUCOSE CONCENTRATION-TIME PROFILES AFTER 4 WEEKS OF TREATMENT WITH METFORMIN XT (2 x 1000 q.d. WITH DINNER) OR GLUCOPHAGE (1 x 1000 mg b.i.d.)
PLASMA GLUCOSE CONC. (mg/dL)
240
220
200
180
160
140
120
0
4
8
12
16
20
24
6 pm
6 am
6 pm
TIME (hr)
METFORMIN XT (n=23)
GLUCOPHAGE (n=23)

FIG. 5

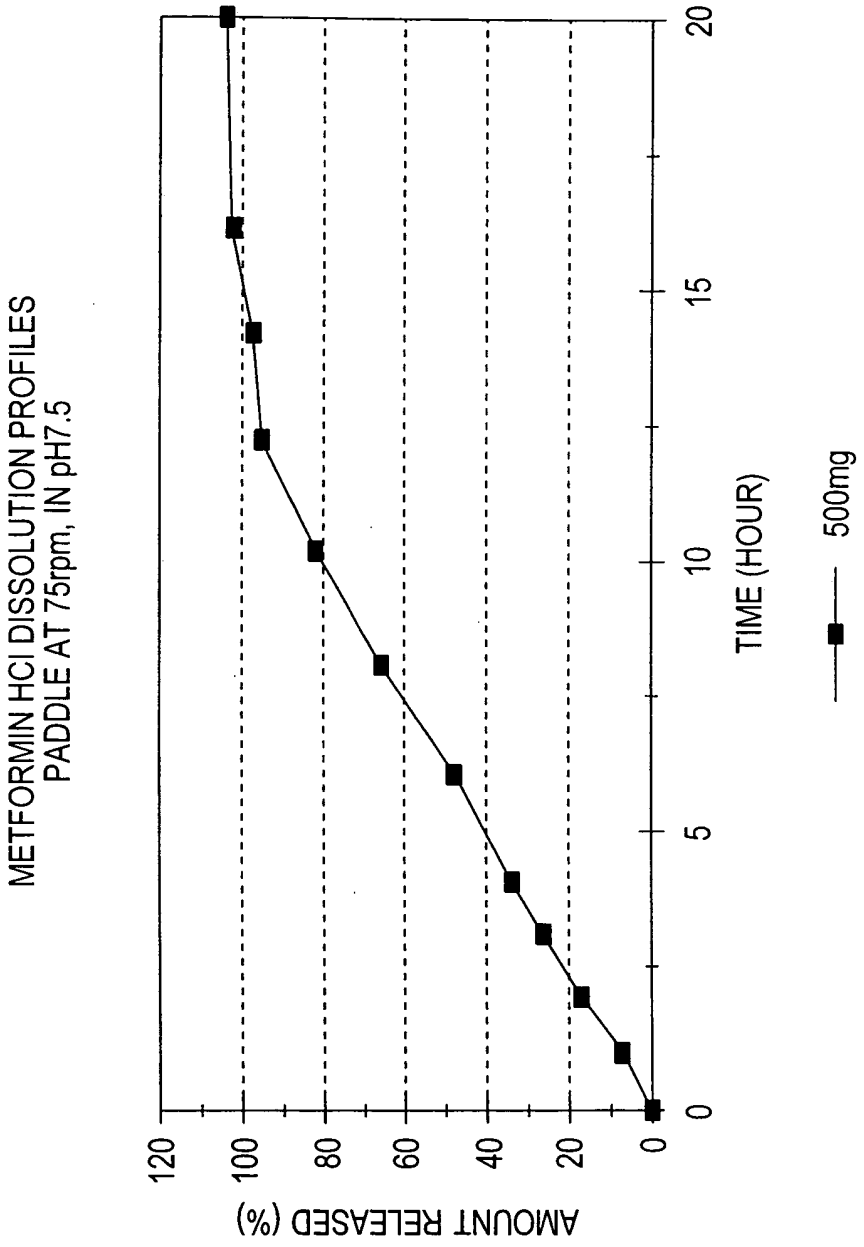
METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
500mg

FIG. 6

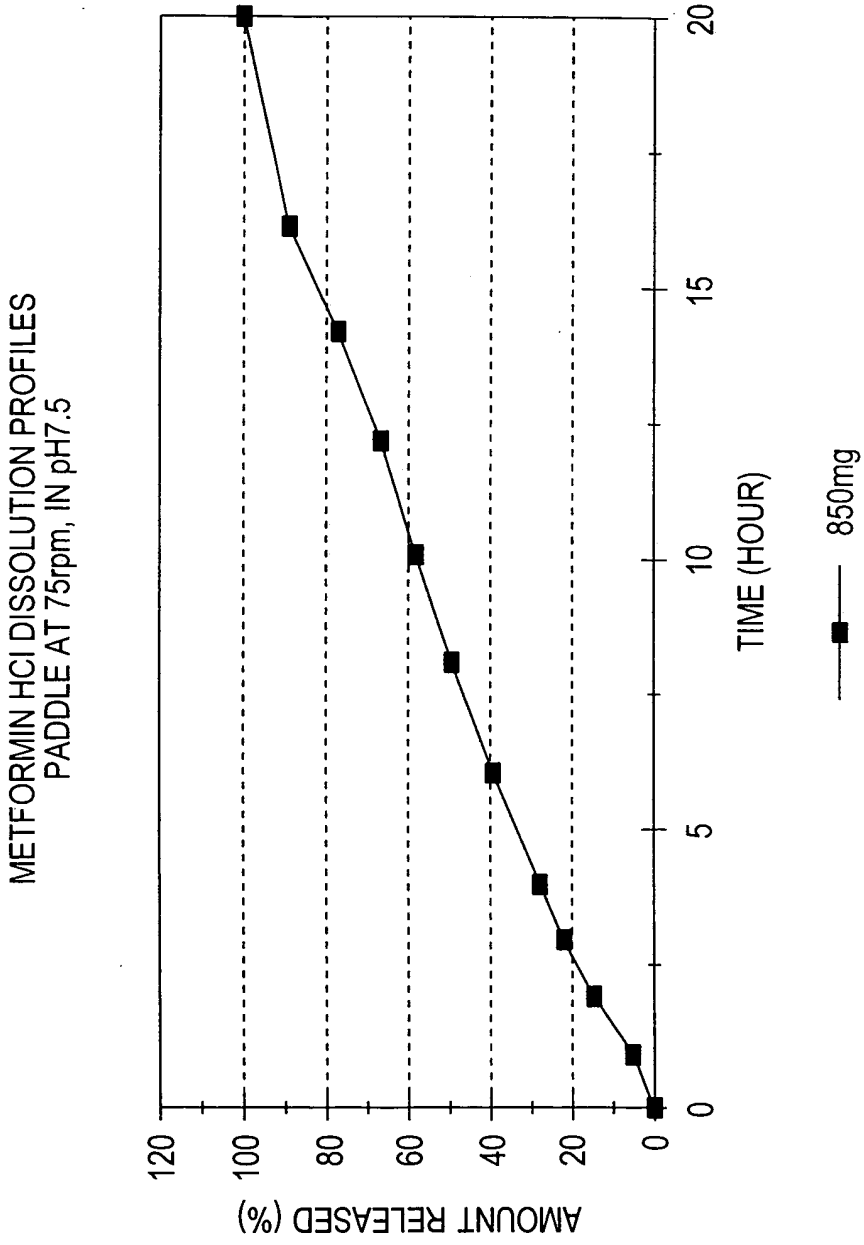
METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
850mg

FIG. 7

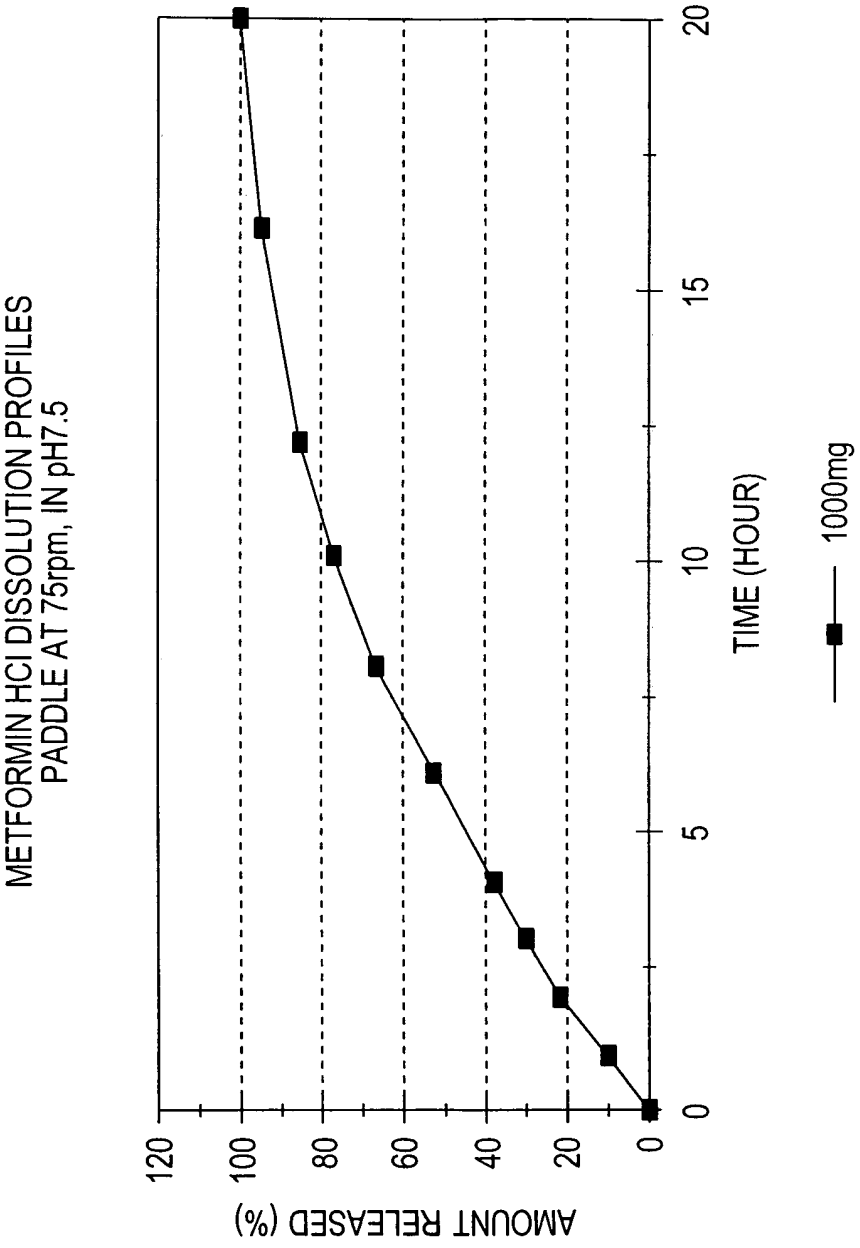
METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
1000mg

FIG. 8

Docket No. 300.1005

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: CONTROLLED RELEASE METFORMIN COMPOSITIONS, the specification of which

___ is attached hereto
X was filed on November 3, 2000 as Application Serial No. 09/705,630 and was amended on _____ (if applicable).
___ I hereby authorize and request our attorney, Davidson, Davidson & Kappel, LLC. of 485 Seventh Avenue, 14th Floor, New York, New York 10018 to insert here in parentheses (Application number _____, filed _____) the filing date and application number of said application when known.

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 all information which is known to me to be material to the patentability of this application as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and/or provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign and/or provisional application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR APPLICATION(S)			Priority claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint Clifford M. Davidson, Registration No. 32,728, Leslye B. Davidson, Registration No. 38,854, Cary S. Kappel, Registration No. 36,561, William C. Gehris, Registration No. 38,156, Morey B. Wildes, Registration No. 36,968, Robert J. Paradiso, Registration No. 41,240, Erik R. Swanson, Registration No. 40,833, Scott L. Appelbaum, Registration No. 41,587, Cynthia R. Moore, Registration No. 46,086, David Knasiak, Registration No. 45,991, Salvatore J. Maiorino, Registration No. 42,830, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; correspondence address: DAVIDSON, DAVIDSON & KAPPEL, LLC, 485 Seventh Avenue, 14th Floor, New York, New York 10018; Telephone: (212) 736-1940; Fax: (212) 736-2427.

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 Chih-Ming Chen

Inventor's signature _____

Date 3/14/01

Residence (city) _____ (state or country) _____

Citizenship UNITED STATES

Post Office Address: _____

Full name of joint Inventor, if any Xiu-Xiu Cheng

Second Inventor's signature _____

Date 3/27/01

Residence (city) _____ (state or country) _____

Citizenship UNITED STATES

Post Office Address: _____

BEST AVAILABLE COPY

Full name of joint Inventor, if any Steve Jan

Third Inventor's signature

Date 3/28/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

Full name of joint Inventor, if any Joseph Chou

Fourth Inventor's signature

Date 3/1/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

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PATENT APPLICATION SERIAL NO _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

09/16/2005 AADOF01 00000019 11225741

01 FC:1011	300.00	OP
02 FC:1111	500.00	OP
03 FC:1311	200.00	OP
04 FC:1202	700.00	OP

PTO-1556
(5/87)

U.S. Government Printing Office: 2002 — 466-247/69033

PTO/SB/06 (12-04)
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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 Effective December 8, 2004

Application or Docket Number: 11225741

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	150.00		N/A	300.00
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	$250		N/A	$500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	$100		N/A	$200
TOTAL CLAIMS (37 CFR 1.16(i))	34 minus 20 =	14	X$ 25 =		OR	X$50 =	700
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	X100 =			X200 =	
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))			+180=			+360=	
			TOTAL			TOTAL	1700

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(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))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(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))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					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.

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 1460, Alexandria, VA 22313-1450.

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

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Serial No.:	To be Assigned
	Application of:	Chih-Ming Chen, et al.
	Filed:	Herewith
	For:	**Controlled Release Metformin Compositions**
	Examiner:	To be Assigned
	Art Unit:	To be Assigned
	Docket No.:	300.1005CON2
	Customer No.:	23280

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

September 13, 2005

PRELIMINARY AMENDMENT

S i r:

Preliminary to examination, please amend the above-identified application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks begin on page 9 of this paper.

AUROBINDO EX. 1017, 306

I. AMENDMENTS TO THE SPECIFICATION

On page 1 of the specification, under the Title of the Invention, please insert the following new paragraph:

--This application is a continuation of U.S. Application Serial No. 10/796,411, filed March 9, 2004, which is a continuation of U.S. Application Serial No. 09/705,630, filed November 3, 2000, now U.S. Patent No. 6,866,866, issued March 15, 2005, the disclosures of which are hereby incorporated by reference in their entireties.--

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II. AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of the Claims

Claims 1-42 (Cancelled)

Claim 43. (New) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 44. (New) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 750 ng/ml to about 1500 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 45. (New) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1125 ng/ml to about 2250 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 46. (New) The controlled release oral dosage form of claim 43, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1875 ng/ml to about 3750 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

AUROBINDO EX. 1017, 308

Claim 47. (New) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form (i) providing an in-vitro dissolution of metformin or salt thereof of from 0-30% at 2 hours when tested in a USP type II apparatus at 75 rpm in 900 mL of pH 7.5 phosphate buffer and at 37 degrees C; and (ii) being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof and providing a mean maximum plasma concentration (C_{max}) of metformin from about 1582 ng/ml to about 3646 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin to human patients.

Claim 48. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 791 ng/ml to about 1823 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 49. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1187 ng/ml to about 2735 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 50. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1978 ng/ml to about 4558 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 51. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2127 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 52. (New) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1064 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

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Claim 53. (New) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1596 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 54. (New) The controlled release oral dosage form of claim 51, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2659 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 55. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2053 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 56. (New) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1027 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 57. (New) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1540 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 58. (New) The controlled release oral dosage form of claim 55, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2566 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 59. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2435 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 60. (New) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1218 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

AUROBINDO EX. 1017, 310

Claim 61. (New) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1827 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 62. (New) The controlled release oral dosage form of claim 59, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3044 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 63. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2288 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 64. (New) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1144 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 65. (New) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1716 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 66. (New) The controlled release oral dosage form of claim 63, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2860 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 67. (New) The controlled release oral dosage form of claim 47, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2849 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

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Claim 68. (New) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 1425 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 69. (New) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 2138 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 70. (New) The controlled release oral dosage form of claim 67, which provides a mean maximum plasma concentration (Cmax) of metformin therapeutically equivalent to 3561 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 71. (New) The controlled release oral dosage form of claim 43, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 72. (New) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 8600 ng/ml to about 16950 ng/ml upon administration of a 1000 mg once-a-day dose of metformin.

Claim 73. (New) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 12900 ng/ml to about 25425 ng/ml upon administration of a 1500 mg once-a-day dose of metformin.

Claim 74. (New) The controlled release oral dosage form of claim 71, which provides a mean $AUC_{0\text{-}24hr}$ of metformin from about 21500 ng/ml to about 42375 ng/ml upon administration of a 2500 mg once-a-day dose of metformin.

Claim 75. (New) The controlled release oral dosage form of claim 43, wherein said dosage form comprising said metformin or pharmaceutically acceptable salt thereof is contained in two formulations.

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Claim 76. (New) The controlled release oral dosage form of claim 43, wherein said core is a tablet core and said membrane comprise a hydrophobic material.

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III. REMARKS

Claims 1-42 have been cancelled. New claims 43-76 have been added.

Support for claim 43 can be found at page 5, line 27 to page 6, line 2; and at page 6, lines 18-21.

Support for claims 44-46 can be found at page 5, line 27 to page 6, line 2; at page 7, lines 4-10; and at page 8, lines 6-9.

Support for claim 47 can be found at page 6, lines 18-24; at page 31, Table 4; and at page 35, Table 6.

Support for claims 48-50 can be found at page 7, lines 4-10; at page 8, lines 6-9; at page 31, Table 4; and at page 35, Table 6.

Support for claims 51 and 55 can be found at page 31, Table 4.

Support for claims 52-54 and claims 56-58 can be found at page 7, lines 4-10; at page 8, lines 6-9; and at page 31, Table 4.

Support for claims 59 and 63 can be found at page 32, Table 5.

Support for claims 60-62 and claims 64-66 can be found at page 7, lines 4-10; at page 8, lines 6-9; and at page 32, Table 5.

Support for claim 67 can be found at page 37, Table 6.

Support for claims 68-70 can be found at page 7, lines 4-10; at page 8, lines 6-9; and at page 37, Table 6.

Support for claim 71 can be found at page 6, lines 5-8.

Support for claims 72-74 can be found at page 6, lines 5-8; at page 7, lines 4-10; and at page 8, lines 6-9.

Support for claim 75 can be found at page 5, lines 6-11.

Support for claim 76 can be found at page 9, lines 6-7; and at page 20, lines 8-10.

It is respectfully submitted that no new matter has been added by virtue of these amendments.

AUROBINDO EX. 1017, 314

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
Title::	Controlled Release Metformin Compositions
Total Drawing Sheets::	8
Formal Drawings::	Yes
Attorney Docket Number::	300.1005CON

Applicant Information

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State or Country of Residence::	Virginia
Postal or Zip Code::	20112
Citizenship Country::	U.S.

AUROBINDO EX. 1017, 316

Correspondence Information

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Telephone::	(212) 736-1940
Fax::	(212) 736-2427
Electronic Mail::	ddk@ddkpatent.com

Representative Information

Representative Customer Number::	23280

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	Continuation of	10/796,411	March 9, 2004
which is a	Continuation of	09/705,630	November 3, 2000

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Name::	Andrx Corporation
Street of mailing address::	8151 Peters Road
City of mailing address::	Plantation
State or Country of Residence::	Florida
Country of mailing address::	U.S.
Postal or Zip Code of mailing address::	33324

AUROBINDO EX. 1017, 317

PTO/SB/06 (12-04)
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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 Effective December 8, 2004

Application or Docket Number: 11/257,741

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	150.00		N/A	300.00
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	$250		N/A	$500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	$100		N/A	$200
TOTAL CLAIMS (37 CFR 1.16(i))	34 minus 20 =	14	X$ 25 =		OR	X$50 =	700
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	X100 =			X200 =	
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))			+180=			+360=	
			TOTAL			TOTAL	1700

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(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))	* 34	Minus	** 34	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					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.

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

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

CLAIMS ONLY

SERIAL NO. 11/229,741

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	/					
2		/				
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TOTAL IND.	2	↓		↓		↓
TOTAL DEP.	49					
TOTAL CLAIMS	49					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51				/		
52				/		
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100			82			
TOTAL IND.		↓		↓		↓
TOTAL DEP.			32			
TOTAL CLAIMS			34			

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2022 (1-88)

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