AO 120 (Rev. 08/10)

TO:	**Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/25/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
SHIONOGI INC. and ANDRX LABS, L.L.C.	AUROBINDO PHARMA LTD. and AUROBINDO PHARMA USA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,790,459	9/14/2004	Andrx Labs, L.L.C.
2	6,866,866	3/15/2005	Andrx Labs, L.L.C.
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

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
09/705,625	11/03/2000	Xiu Xiu Cheng	141-603

CONFIRMATION NO. 6705

POA ACCEPTANCE LETTER

96056
Florek & Endres PLLC
1156 Avenue of the Americas
Suite 600
New York, NY 10036

OC000000044246696

Date Mailed: 10/29/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/22/2010.

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.

/vvan/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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
09/705,625	11/03/2000	Xiu Xiu Cheng	141-603

CONFIRMATION NO. 6705

POWER OF ATTORNEY NOTICE

47888
HEDMAN & COSTIGAN, P.C.
1230 AVENUE OF THE AMERICAS
7th floor
NEW YORK, NY 10020

OC00000044246610

Date Mailed: 10/29/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/22/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/vvan/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 96056

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 96056

OR

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

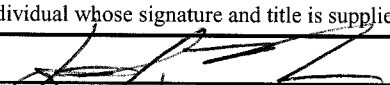
Assignee Name and Address:

Andrx Labs, LLC
4955 Orange Drive
Davie, Florida 33314

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	September 20, 2010
Name	David A. Buchen	Telephone	
Title	Senior VP/ General Counsel		

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.**

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

Electronic Acknowledgement Receipt

EFS ID:	8684580
Application Number:	09705625
International Application Number:	
Confirmation Number:	6705
Title of Invention:	METHODS FOR TREATING DIABETES VIA ADMINISTRATRION OF CONTROLLED RELEASE METFORMIN
First Named Inventor/Applicant Name:	Xiu Xiu Cheng
Customer Number:	47888
Filer:	Matthew J Solow/jonathan goodman
Filer Authorized By:	Matthew J Solow
Attorney Docket Number:	141-603
Receipt Date:	22-OCT-2010
Filing Date:	03-NOV-2000
Time Stamp:	15:38:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73(b).	6790459statement.pdf	73842 4f7cf085fe48c54331fb95ebf3da307c8c460ef6	no	1

Warnings:	
Information:	

2	Power of Attorney	AndrxLabsPOA.pdf	171203 a2c5c2c827e09c383c1e79893ffb0cc5247af0d9	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	245045

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Xiu Xiu Cheng, Chih-Ming Chen, Steve Jan, Joseph Chou

Application No./Patent No.: 6,790,459 Filed/Issue Date: September 14, 2004

Titled: METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

Andrx Labs, LLC , a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

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 therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: X. Cheng, C.Chen, S. Jan, J.Chou To: ANDRX CORPORATION

The document was recorded in the United States Patent and Trademark Office at
Reel 011687, Frame 0690, 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(s).

[X] 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.

Signature — October 15, 2010 (Date)

David A. Buchen — Printed or Typed Name

Senior VP/ 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.

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
09/705,625	11/03/2000	Xiu Xiu Cheng	141-603

CONFIRMATION NO. 6705

OC000000025208359

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

Date Mailed: 08/06/2007

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/23/2007.

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.

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

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
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012

CONFIRMATION NO. 6705

OC000000025208332

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

Date Mailed: 08/06/2007

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/23/2007.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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

PTO/SB/21 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	3

Application Number	09/705,625
Filing Date	November 3, 2000
First Named Inventor	Cheng et al.
Art Unit	1615
Examiner Name	T. Ware
Attorney Docket Number	141-603

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

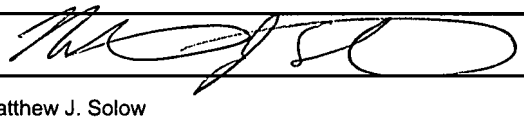
Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Matthew J. Solow		
Date	July 19, 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 19, 2007

PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/705,625
Filing Date	November 3, 2000
First Named Inventor	Cheng et al.
Title	Methods for Treating Diabetes Via....
Art Unit	1615
Examiner Name	T. Ware
Attorney Docket Number	141-603

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	July 12, 2007
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.

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

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Xiu Xiu Cheng et al.

Application No./Patent No.: 6,790,459 Filed/Issue Date: September 14, 2004

Entitled: METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

Andrx Labs, LLC, a Limited Liability Company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is_____ %)

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Xiu Xiu Cheng et al. To: Andrx Corporation
The document was recorded in the United States Patent and Trademark Office at
Reel 011687, Frame 0690, 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 — Signature
July 12, 2007 — Date
Roberta Loomar — Printed or Typed Name
954-762-6211 — Telephone Number
Vice President, Chief Compliance Officer and Assistant General Counsel — Title

300.1012

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicants:	Xiu Xiu CHENG, et al.
Serial No.:	09/705,625
Filed:	November 3, 2000
For:	**METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**
Art Unit:	1615

RESPONSE TO NOTICE REGARDING DRAWINGS

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

August 2, 2004

Sir:

In response to the Notice Regarding Drawings, dated June 21, 2004, Applicants submit replacement drawings, Figures 1-8.

If any additional fees are deemed to be due at this time, the Commissioner is authorized to charge payment of the same to Deposit Account No. 50-0552.

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, NY 10018
(212)736-1940

FORM PTO-1083

Docket No.: 300.1012
Date: August 2, 2004

1615
95
B

COMMISSIONER FOR PATENTS
P.O. BOX 1450
Alexandria, VA 22313-1450

In re application of: Xiu Xiu CHENG, et al.
Serial No.: 09/705,625
Filed: November 3, 2000
For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

S i r:

Transmitted herewith is a **Response to Notice Regarding Drawings** in the above-identified application.

[] Small entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a verified statement previously submitted.
[] A verified statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.
[X] No fee for additional claims is required.
[] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus 20** =			x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus 3*** =	0		x $ 42	$		x $ 84	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $140	$		+ $280	$
				TOTAL: $		OR	TOTAL: $	

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[X] Also transmitted herewith are:
[ ] Petition for one-month extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Eight sheets of drawings**

[ ] Check(s) in the amounts of **$.00** is/are attached to cover:
[] Filing fee for additional claims under 37 C.F.R. 1.16
[] Petition fee for one month extension under 37 C.F.R. 1.136
[X] Other:

[X] The Assistant 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. A duplicate copy of this sheet is enclosed.
[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
(212) 736-1940

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are 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 August 2, 2004.

DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: Guendoline Decosta
Guendoline Decosta

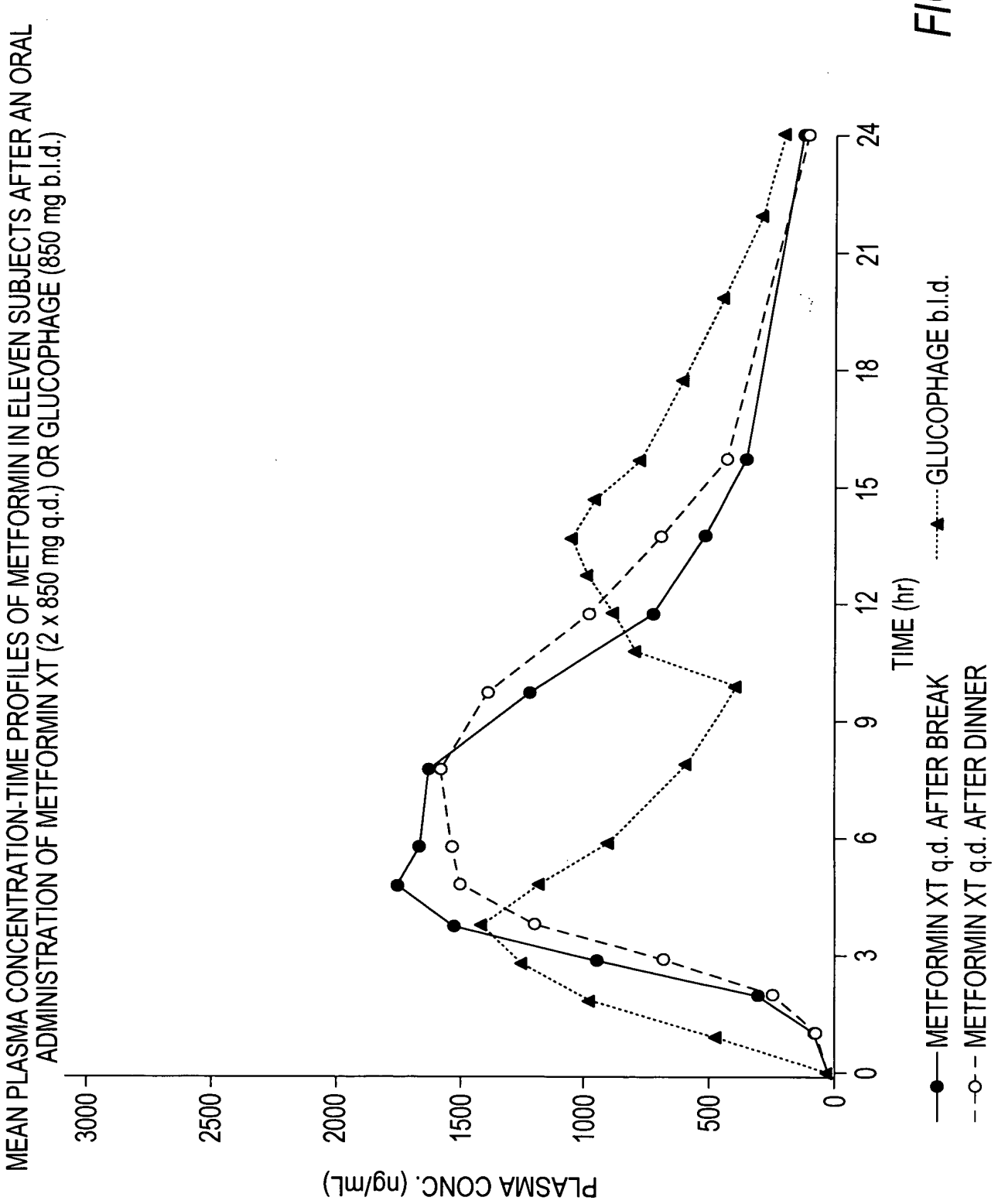


FIG. 1

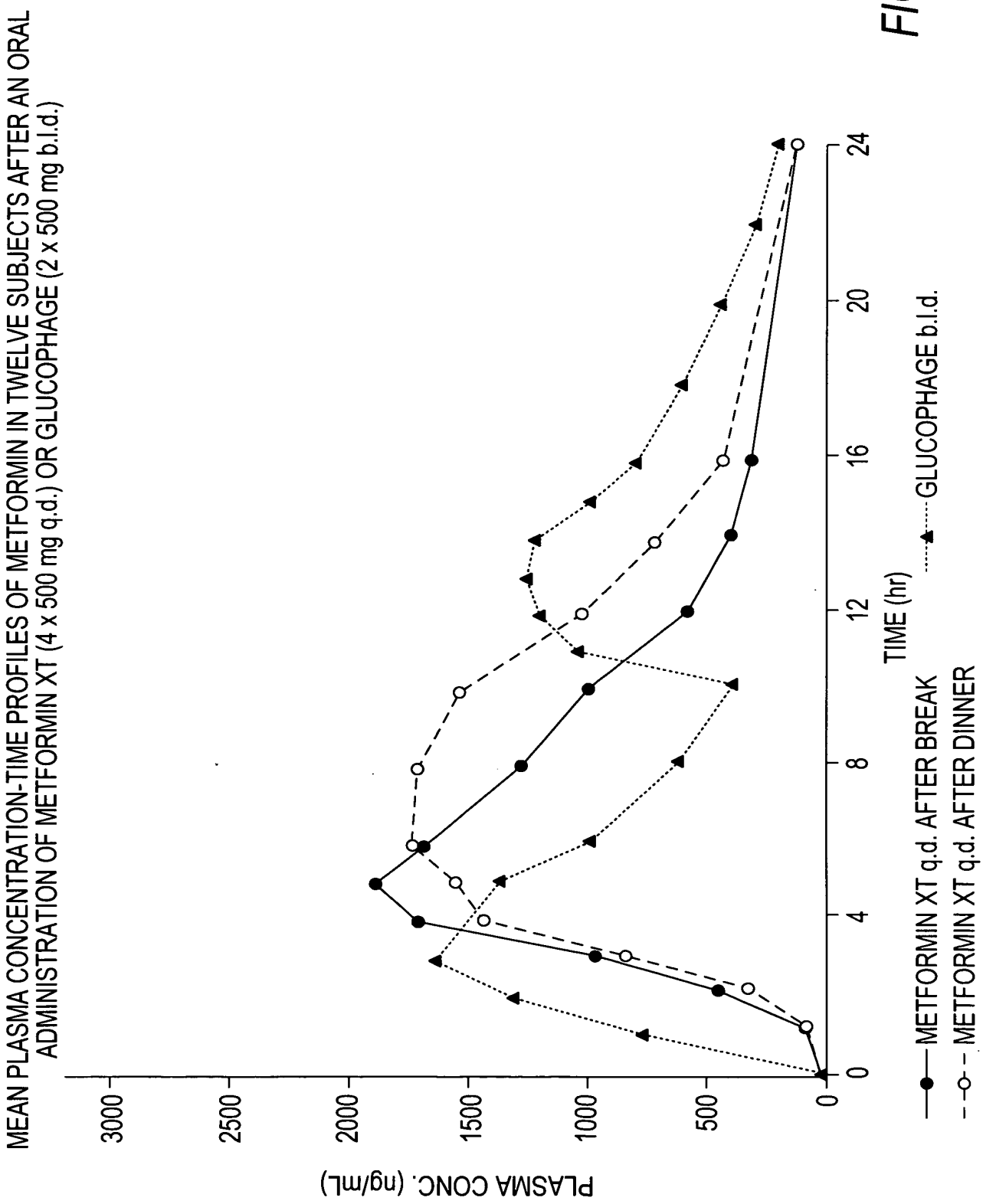


FIG. 2

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN EIGHT HEALTHY SUBJECTS AFTER MULTIPLE ORAL DOSES OF METFORMIN XT (4 x 500 mg q.d.)

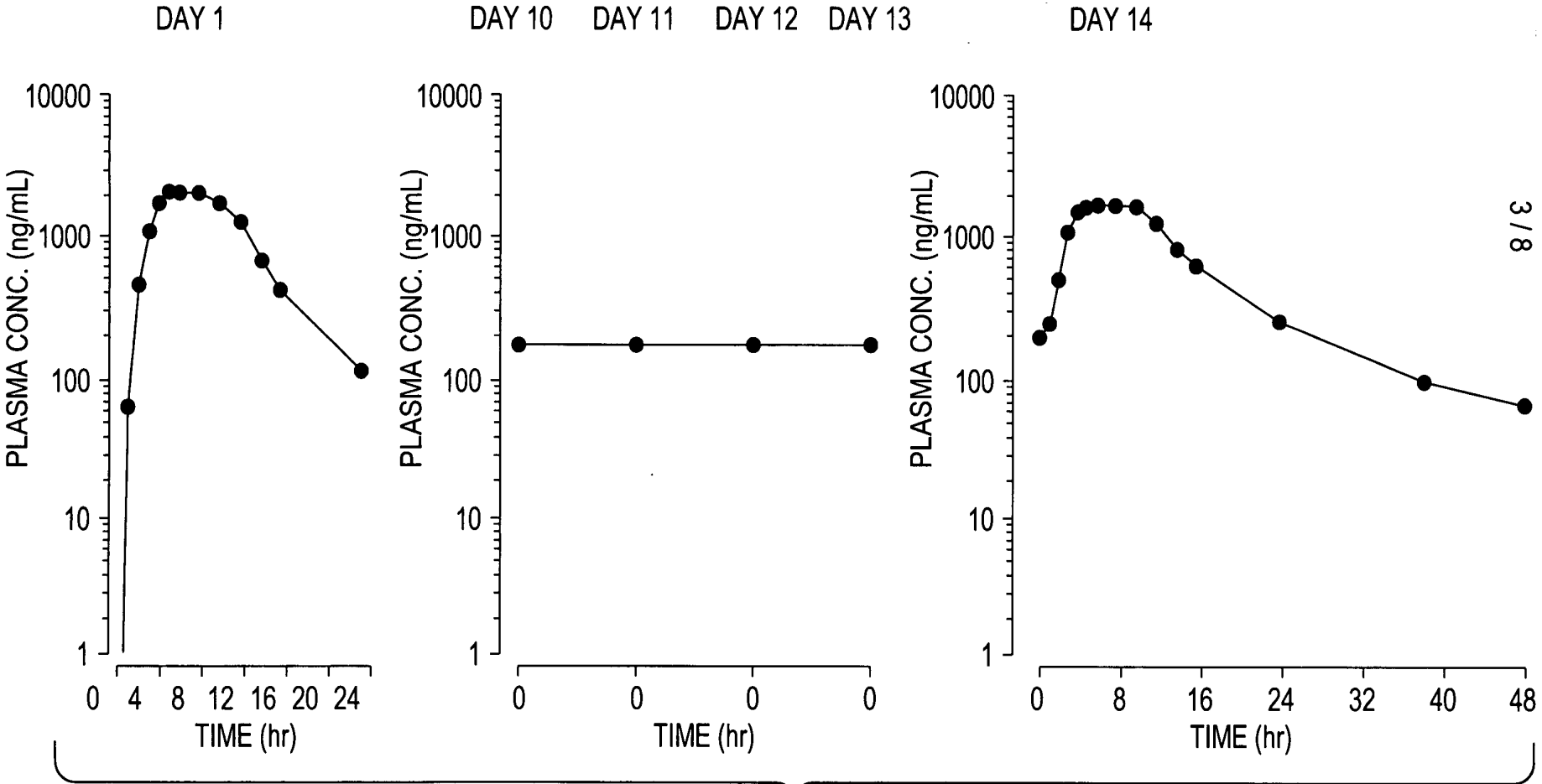


FIG. 3

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN
Inventor: Xiu Xiu Cheng, et al.
Application Serial No.: 09/705,625

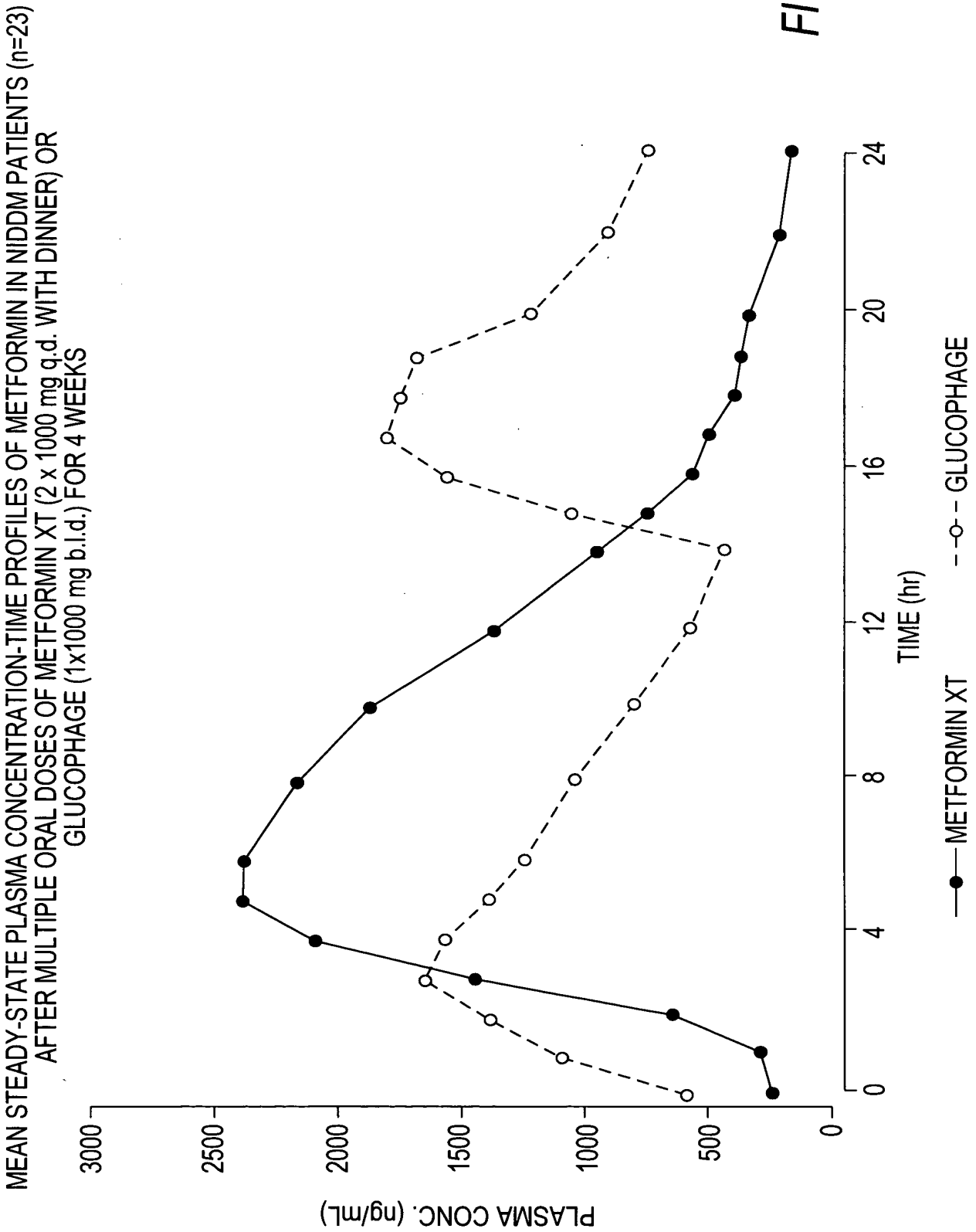


FIG. 4

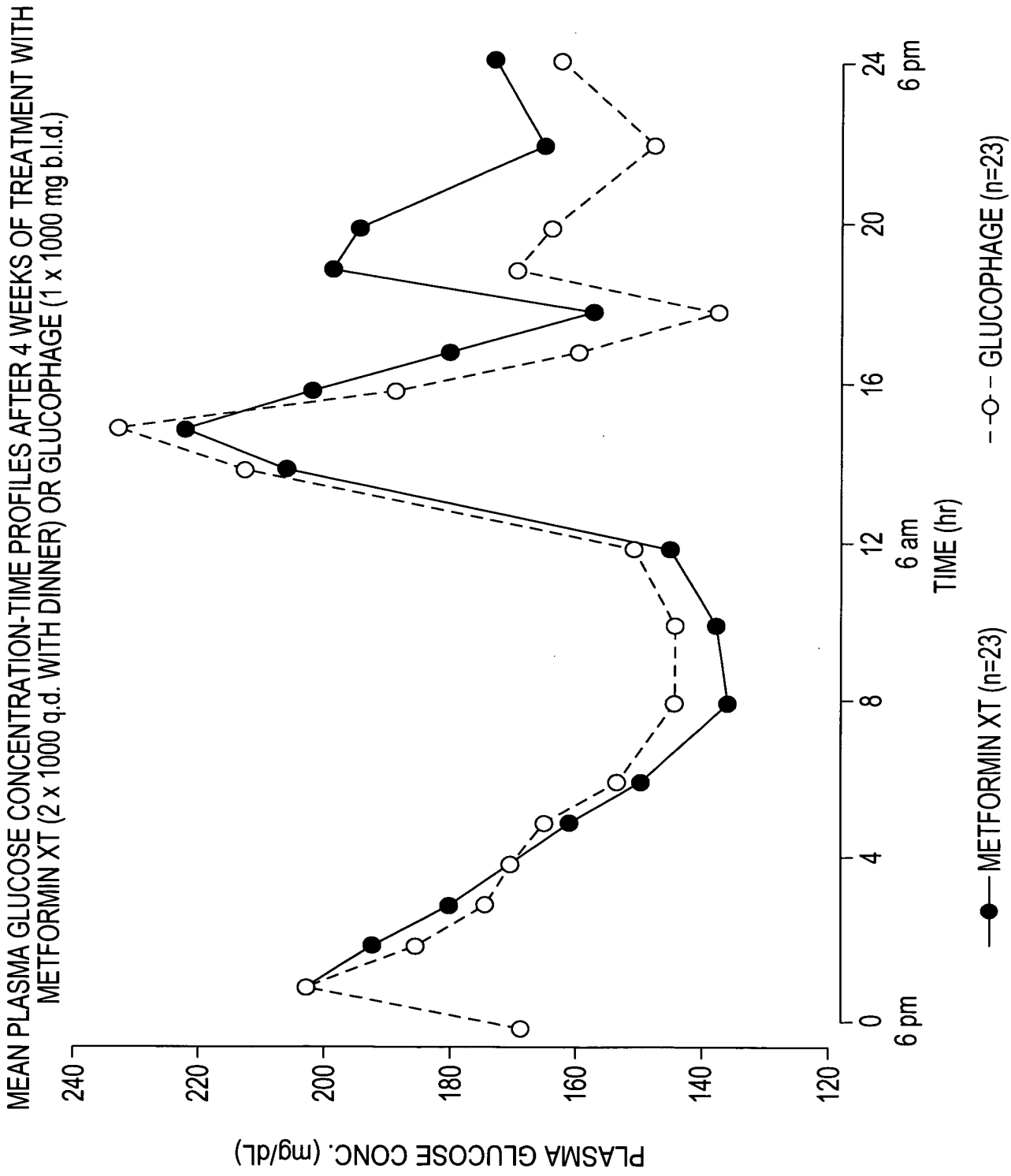


FIG. 5

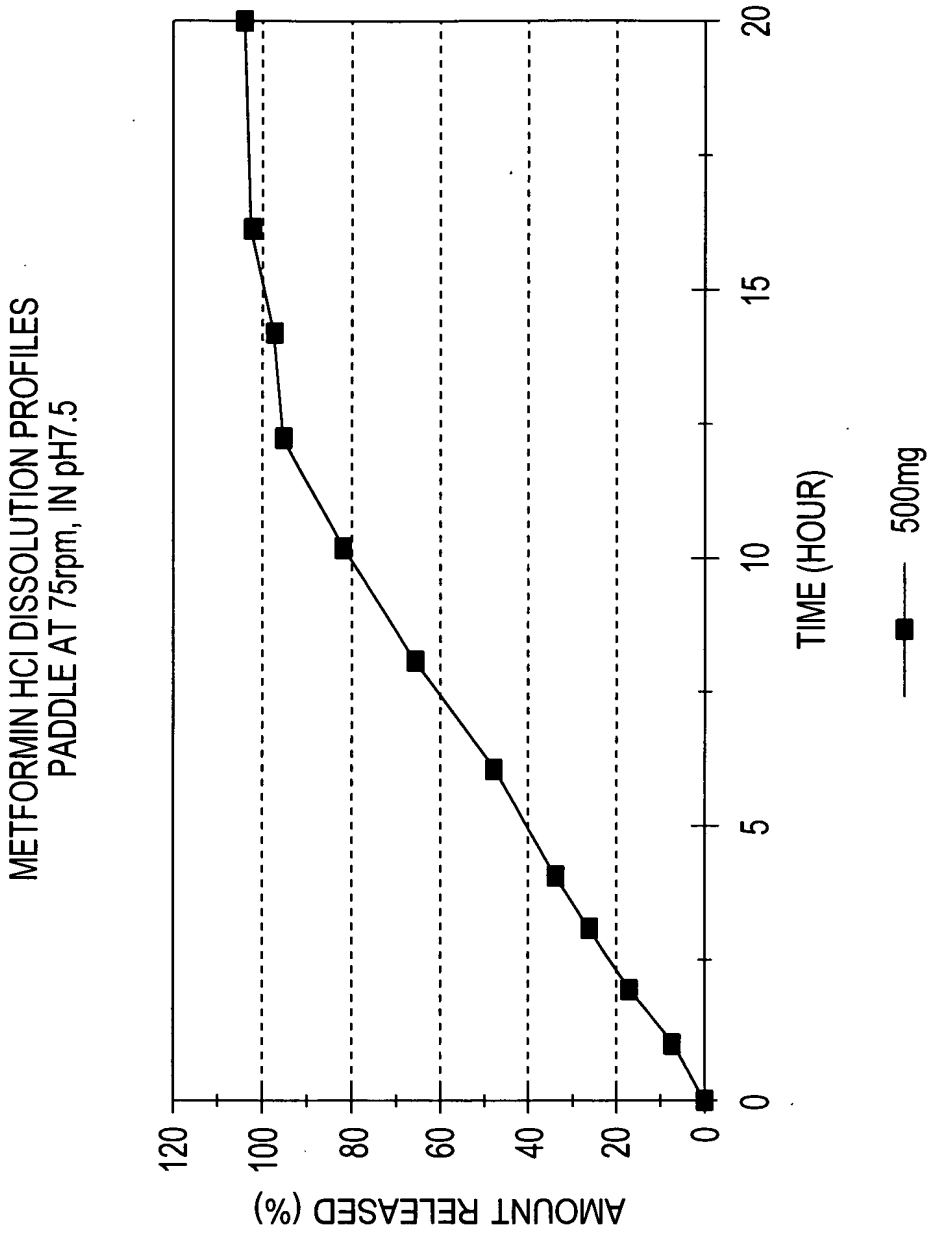


FIG. 6

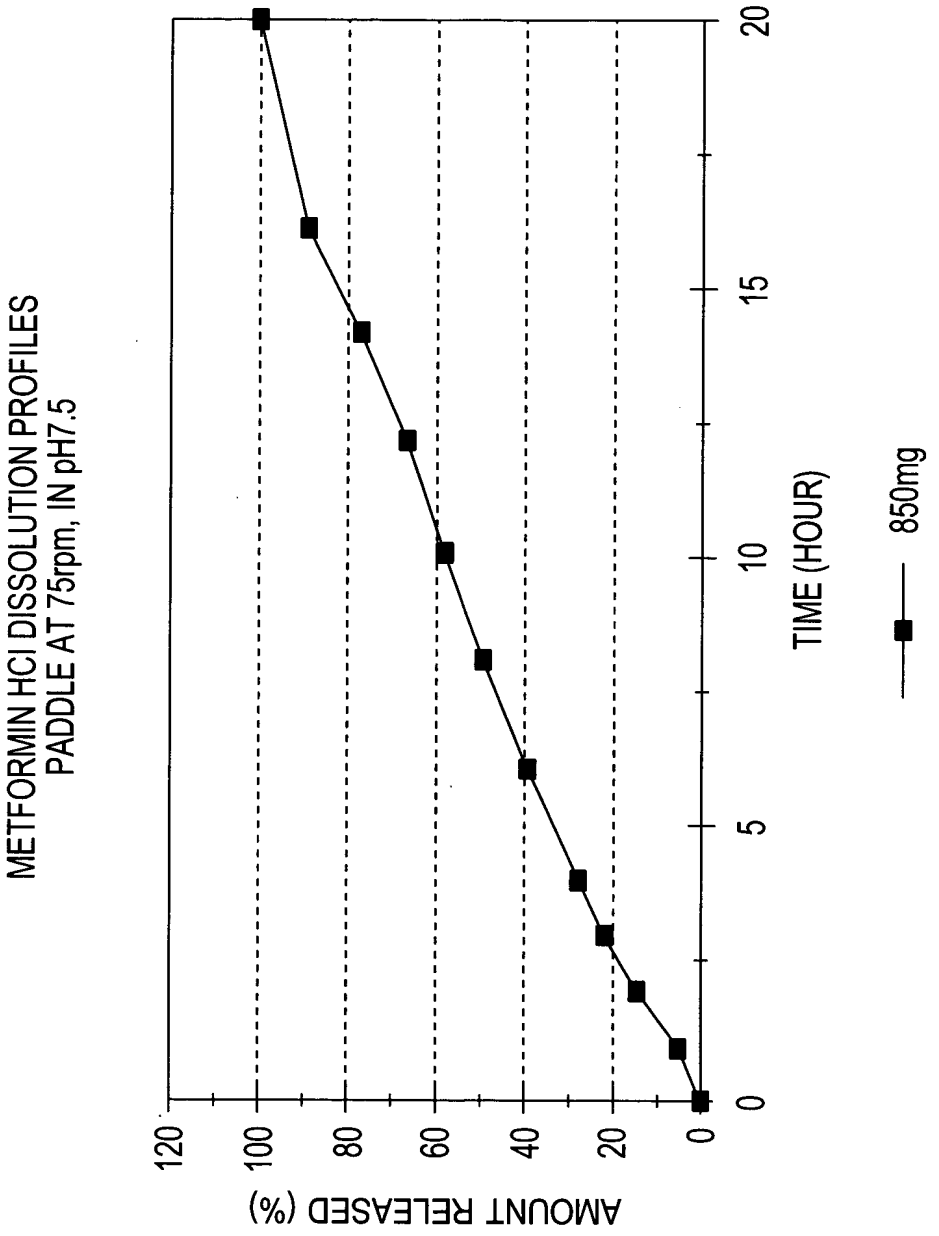


FIG. 7

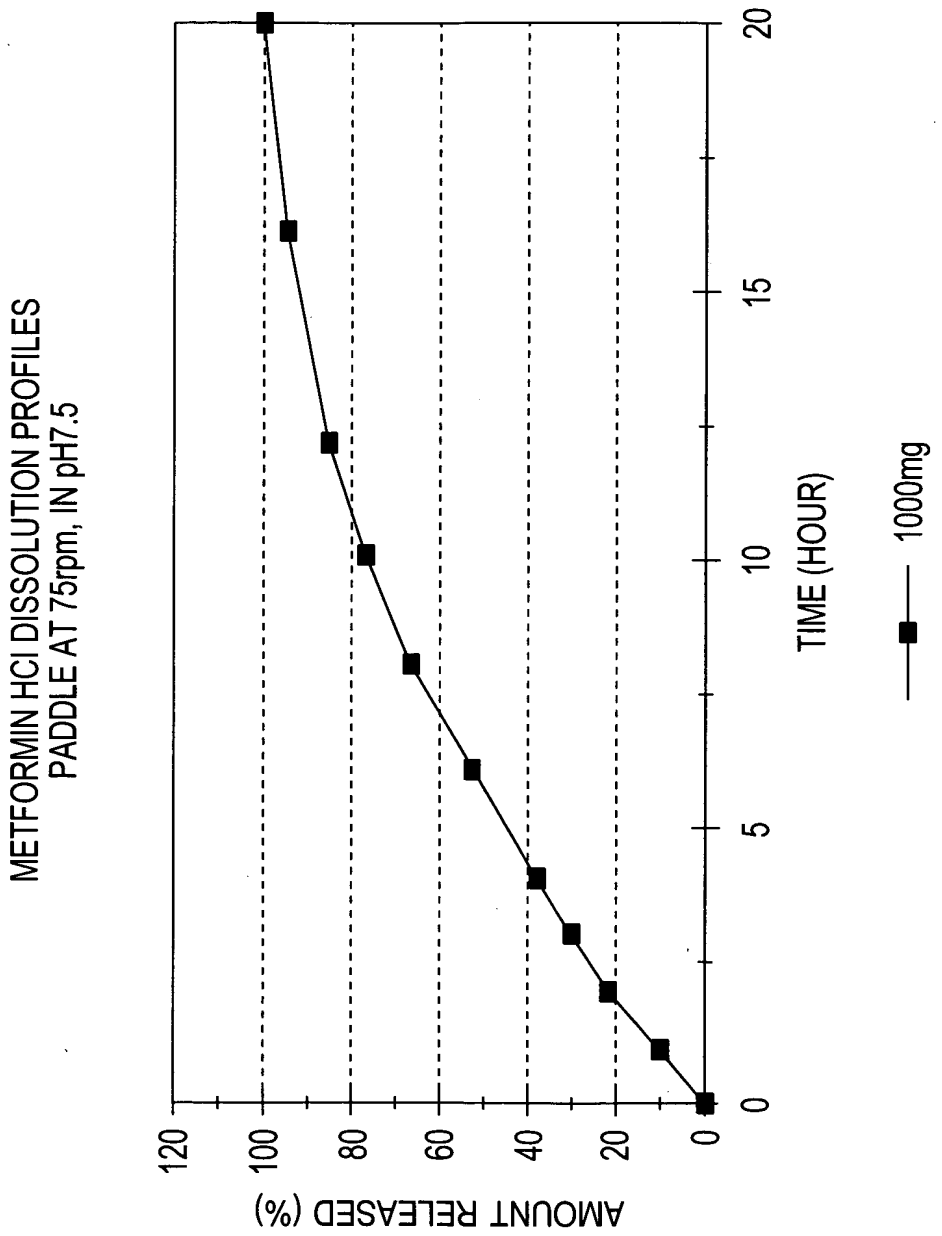


FIG. 8

H.C Pat Rec

*RETURN TO FMF - LOCATION 7540

QUERY CONTROL FORM				RTIS USE ONLY
Application No. 09705625	Prepared by	DG		Tracking Number
Examiner-GAU Tran - 1615	Date	6-2-04		Week Date
	No. of queries	1 (A)		

Attn: Chief Drafts person

JACKET

a. Serial No.	f. Foreign Priority	k. Print Claim(s)	p. PTO-1449
b. Applicant(s)	g. Disclaimer	l. Print Fig.	q. PTOL-85b
c. Continuing Data	h. Microfiche Appendix	m. Searched Column	r. Abstract
d. PCT	i. Title	n. PTO-270/328	(s.) Sheets/Figs
e. Domestic Priority	j. Claims Allowed	o. PTO-892	t. Other

SPECIFICATION

a. Page Missing
b. Text Continuity
c. Holes through Data
d. Other Missing Text
e. Illegible Text
f. Duplicate Text
g. Brief Description
h. Sequence Listing
i. Appendix
j. Amendments
k. Other

CLAIMS

a. Claim(s) Missing
b. Improper Dependency
c. Duplicate Numbers
d. Incorrect Numbering
e. Index Disagrees
f. Punctuation
g. Amendments
h. Bracketing
i. Missing Text
j. Duplicate Text
k. Other

MESSAGE Sheets/Figs: Copy mark: Figs 1-8.

Please Resolve.

Thank You

initials DG

RESPONSE SEE ATTACHMENT

948

initials JJC

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMES APPLICANT	ATTORNEY DOCKET NUMBER
09/705625	11/03/2000	CHENG, XIU XIU	300.1012

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

Examiner
TRAN, SUSAN

Art Unit
1615

Paper Number

Date Mailed: **06-21-04**

Notice Regarding Drawings

Corrected drawings for the above-identified application, received in the USPTO on **11-3-00** are still not acceptable for the reason(s) identified on the attached PTO-948. Applicant is given one opportunity to correct the informalities within a two-month time period from the mailing date of this Notice. **THIS TIME PERIOD IS NOT EXTENDABLEUNDER EITHER 37 CFR 1.136(a) OR 1.136(b). Failure to take corrective action within the set period will result in abandonment of the application.**

ATTACHMENT: PTO-948 Notice of Draftsperson's Patent Review

RETURN CORRECTED DRAWINGS TO:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Joshua D. Chase
Office of Patent Publication,
Publishing Division
703-305-8430

Form PTO-948 (Rev. 06/03)
Application No. 9/705,625

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 11-3-00 are:

A. ___ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ✓ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. Corrected drawings are required.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink or Color (3 sets required).

___ Color drawings are not acceptable until petition is granted. Fig(s)___

___ Pencil and non black ink not permitted. Fig(s)___

2. PHOTOGRAPHS. 37 CFR 1.84(b)

___ One (1) full-tone set is required. Fig(s)___

___ Photographs may not be mounted. 37 CFR 1.84(e)

___ Photographs must meet paper size requirements of 37 CFR 1.84(f). Fig(s)___

___ Poor quality (half-tone). Fig(s)___

3. TYPE OF PAPER. 37 CFR 1.84(e)

___ Paper not flexible, strong, white, and durable. Fig(s)___

✓ Erasures, alterations, overwritings. interlineations, folds, copy machine marks not accepted. Fig(s) 1-8

4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:

21.0 cm by 29.7 cm (DIN size A4) or
21.6 cm by 27.9 cm (8 1/2x 11 inches)

___ All drawing sheets not the same size. Sheet(s)___

___ Drawings sheets not an acceptable size. Fig(s)___

5. MARGINS. 37 CFR 1.84(g): Acceptable margins: Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm

✓ Margins not acceptable. Fig(s) 1-4,6-8

✓ Top (T) ✓ Left (L)

___ Right (R) ___ Bottom (B)

6. VIEWS. 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes, e.g., if Fig. 1 is changed to Fig. 1A, Fig 1B and Fig. 1C, etc., the specification, at the Brief Description of the Drawings, must likewise be changed.

___ Views not labeled separately or properly. Fig(s)___

7. SECTIONAL VIEWS. 37 CFR 1.84(h)(3)

___ Sectional designation should be noted with Arabic or Roman numbers. Fig(s)___

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)

___ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)___

9. SCALE. 37 CFR 1.84(k)

___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)___

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)

✓ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) 6-8

11. SHADING. 37 CFR 1.84(m)

___ Solid black areas pale. Fig(s) ___

___ Solid black shading not permitted. Fig(s)___

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)

___ Numbers and reference characters not plain and legible. Fig(s)___

✓ Figure legends are poor. Fig(s) 1-8

___ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s)___

___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)___

___ Numbers, letters and reference characters must be at least 32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3). Fig(s)___

13. LEAD LINES. 37 CFR 1.84(q)

___ Lead lines missing. Fig(s)___

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)

___ Sheets not numbered consecutively, and in Arabic numbers beginning with number 1. Sheet(s)___

15. NUMBERING OF VIEWS. 37 CFR 1.84(u)

___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)___

16. DESIGN DRAWINGS. 37 CFR 1.152

___ Surface shading shown not appropriate. Fig(s)___

___ Solid black surface shading is not permitted except when used to represent the color black as well as color contrast. Fig(s)___

COMMENTS:

Reviewer J. CHASE

Date 6-21-04

If you have questions, call (703) 305-8404.

Attachment to Paper No. ___

Best Available Copy

☆ U.S. GOVERNMENT PRINTING OFFICE: 2003-300-153

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

23280 7590 02/11/2004

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

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

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

Calvin Ashby III	(Depositor's name)
Calv Ashby III	(Signature)
April 29, 2004	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

TITLE OF INVENTION: METHODS FOR TREATING DIABETES VIA ~~ADMINISTRATRION~~ ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	~~$1330~~ $1360	05/11/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAN, SUSAN T	1615	424-468000

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

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

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

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Davidson, Davidson & Kappel, LLC
2
3

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Andrx Labs, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Davie, Florida

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☒ corporation or other private group entity ☐ government

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

☒ Issue Fee

☐ Publication Fee

☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

☒ A check in the amount of the fee(s) is enclosed.

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

☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 50-0552 (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date) April 29, 2004

Robert J. Paradiso, Reg. No. 41,240

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

05/04/2004 WABRHAM2 00000058 09705625

01 FC:1501 1330.00 OP
02 FC:8001 30.00 OP

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

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

TRANSMIT THIS FORM WITH FEE(S)

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

23280 7590 02/11/2004

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

EXAMINER	
TRAN, SUSAN T	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 02/11/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

TITLE OF INVENTION: METHODS FOR TREATING DIABETES VIA ADMINISTRATRION OF CONTROLLED RELEASE METFORMIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/11/2004

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

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

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

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

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

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

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

23280 7590 02/11/2004

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

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

Certificate of Mailing or Transmission

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

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

TITLE OF INVENTION: METHODS FOR TREATING DIABETES VIA ADMINISTRATRION OF CONTROLLED RELEASE METFORMIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/11/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAN, SUSAN T	1615	424-468000

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

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

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

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

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

Please check the appropriate assignee category or categories (will not be printed on the patent); ❑ individual ❑ corporation or other private group entity ❑ government

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

❑ Issue Fee

❑ Publication Fee

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.

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

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

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

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

TRANSMIT THIS FORM WITH FEE(S)

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.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

23280 7590 02/11/2004

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

EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 02/11/2004

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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

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

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

Notice of Allowability	Application No.	Applicant(s)	
	09/705,625	CHENG ET AL.	
	Examin r	Art Unit	
	Susan T. Tran	1615	

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

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

1. ☒ This communication is responsive to *Amendment filed 07/14/03 and Remarks filed 12/01/03*.
2. ☒ The allowed claim(s) is/are *1,4,5,7-11,14,15,18,22,26-31 and 35-37*.
3. ☒ The drawings filed on *11/03/00* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

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

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the margin according to 37 CFR 1.121(d).
9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No. _____
4☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5☐ Notice of Informal Patent Application (PTO-152)
6☐ Interview Summary (PTO-413), Paper No._____ .
7☐ Examiner's Amendment/Comment
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other .

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
AU 1615

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
300.1012	09/705,625
APPLICANTS: Chih-Ming CHEN, et al.	
FILING DATE: November 3, 2000	GROUP: 1614 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
S.T	AA	6	0	1	0	7	1	8		1/4/00	Al-Razzak et al.	424	464	
	AB	5	8	5	8	3	9	8		1/12/99	Cho	424	450	
	AC	5	6	9	1	3	8	6		11/25/97	Inman et al.	514	691	
	AD	5	6	8	8	5	1	8		11/18/97	Ayer et al.	424	422	
	AE	5	6	7	4	9	0	0		10/7/97	Ubillas et al.	514	557	
	AF	5	6	6	8	1	1	7		9/16/97	Shapiro	514	55	
	AG	5	6	6	7	8	0	4		9/16/97	Wong et al.	424	472	
	AH	5	6	5	0	1	7	0		7/22/97	Wright et al.	424	473	
	AI	5	6	3	1	2	2	4		5/20/97	Efendic et al.	514	12	
S.T	AJ	5	6	2	9	3	1	9		5/13/97	Luo et al.	514	284	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
S.T	AK	9	9	4	7	1	2	8		9/23/99	WO	A61K	9/24		
S.T	AL	9	9	4	7	1	2	5		9/23/99	WO	A61K	9/20		
S.T	AM	9	9	2	9	3	1	4		6/17/99	WO	A61K	31/155		
S.T	AN	9	6	0	8	2	4	3		3/21/96	WO	A61K	31/155		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

S.T	AO	*Physicians' Desk Reference* (54th Ed. 2000), pp. 831-835.
S.T	AP	Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371.
S.T	AQ	Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.
S.T	AR	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.
S.T	AS	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 James M. Spear DATE CONSIDERED 1-28-04

*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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1012	SERIAL NO. 09/705,625
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE November 3, 20000	GROUP ~~1614~~ 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
S.T	BA	5	6	1	4	5	7	8		3/25/97	Dong et al.	524	377	
	BB	5	5	9	1	4	5	4		1/7/97	Kuczynski et al.	424	486	
	BC	5	5	4	5	4	1	3		8/13/96	Kuczynski et al.	424	473	
	BD	5	5	4	3	1	5	6		8/6/96	Roorda et al.	424	484	
	BE	5	5	1	2	2	9	3		4/30/96	Landrau et al.	424	449	
	BF	5	4	1	3	5	7	2		5/9/95	Wong et al.	604	892.1	
	BG	5	3	0	8	3	4	8		5/3/94	Balaban et al.	604	892.1	
	BH	5	1	8	5	1	5	8		2/9/93	Ayer et al.	424	473	
	BI	5	1	7	8	8	6	7		1/12/93	Guittard et al.	424	473	
	BJ	5	1	4	1	7	5	2		8/25/92	Ayer et al.	424	473	
	BK	5	1	2	0	5	4	8		6/9/92	McClelland et al.	424	473	
	BL	5	1	1	0	5	9	7		5/5/92	Wong et al.	424	438	
	BM	5	0	9	1	1	9	0		2/25/92	Kuczynski et al.	424	473	
	BN	5	0	7	1	6	0	7		12/10/91	Ayer et al.	264	112	
	BO	5	0	2	4	8	4	3		6/18/91	Kuczynski et al.	514	255.06	
	BP	4	9	6	3	1	4	1		10/16/90	Eckenhoff	604	892.1	
	BQ	4	8	9	2	7	3	9		1/9/90	Shah et al.	424	473	
S.T	BR	4	8	6	5	5	9	8		9/12/89	Eckenhoff	604	892.1	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	BS														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	BT	

EXAMINER S.T	DATE CONSIDERED 1/28/04

*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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1012	SERIAL NO. 09/705,625
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP ~~1614~~ 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
S.T	CA	4	8	5	1	2	2	9		7/25/89	Magruder et al.	424	457	
	CB	4	7	8	3	3	3	7		11/8/88	Wong et al.	424	468	
	CC	4	7	7	7	0	4	9		10/11/88	Magruder et al.	424	457	
	CD	4	7	0	4	1	1	8		11/3/87	Eckenhoff	424	438	
	CE	4	6	9	2	3	3	6		9/8/87	Eckenhoff et al.	424	468	
	CF	4	6	2	7	8	5	0		12/9/86	Deters et al.	604	892.1	
	CG	4	6	2	4	8	4	7		11/25/86	Ayer et al.	424	467	
	CH	4	6	1	5	6	9	8		10/7/86	Guittard et al.	604	892.1	
	CI	4	6	1	2	0	0	8		9/16/86	Wong et al.	604	892.1	
	CJ	4	6	0	9	3	7	4		9/2/86	Ayer	424	473	
	CK	4	5	8	7	1	1	7		5/6/86	Edgren et al.	424	473	
	CL	4	5	2	2	6	2	5		6/11/85	Edgren	424	473	
	CM	4	1	1	1	2	0	1		9/5/78	Theeuwes	424	473	
	CN	4	0	8	8	8	6	4		5/9/78	Theeuwes et al.	219	121.71	
	CO	4	0	8	0	4	7	2		3/21/78	Bohuon	514	555	
	CP	4	0	7	7	4	0	7		3/7/78	Theeuwes et al.	424	427	
S.T	CQ	4	0	6	3	0	6	4		12/13/77	Saunders et al.	219	121.7	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	CR														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	CS	

EXAMINER S.T	DATE CONSIDERED 1/28/04

*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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
300.1012	09/705,625
APPLICANTS: Chih-Ming CHEN, et al.	
FILING DATE November 3, 2000	GROUP ~~1614~~ 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
S.T	DA	4	0	3	6	2	2	8	7/19/77	Theeuwes	424	473	
	DB	4	0	3	4	7	5	8	7/12/77	Theeuwes	424	427	
	DC	4	0	0	8	7	1	9	2/22/77	Theeuwes et al.	424	427	
	DD	3	9	5	7	8	5	3	5/18/76	Bohuon	560	143	
	DE	3	9	5	2	7	4	1	4/27/76	Baker	424	405	
	DF	3	9	1	6	8	9	9	11/4/75	Theeuwes et al.	424	424	
S.T	DG	3	8	4	5	7	7	0	11/5/74	Theeuwes et al.	424	427	
	DH												
	DI												
	DJ												
	DK												
	DL												
	DM												
	DN												
	DO												
	DP												
	DQ												

FOREIGN PATENT DOCUMENTS

				DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
								YES	NO
	DR								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	DS	

EXAMINER	S.T	DATE CONSIDERED	1/28/04

*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.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1012	SERIAL NO.: 09/705,625
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Xiu Xiu CHENG, et al.	
		FILING DATE: November 3, 2000	GROUP: 1615

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
S.T	AA	6 4 7 5 5 2 1	11/05/2002	Timmins et al.	424	469	Sep. 16, 1999
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AH							
	AI							
	AJ							
	AK							
	AL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

~~—~~	~~AM~~	~~Andrx Pilot Biostudy Data (20 pages)~~ No date
	AN	
	AO	
	AP	
	AQ	
	AR	
	AS	

EXAMINER	DATE CONSIDERED
S.T	01/28/04

*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.

Issue Classification	Application No.	Applicant(s)	
	09/705,625	CHENG ET AL.	
	Examiner	Art Unit	
	Susan T. Tran	1615	

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
424	468	424	464	465	469	470	472	474	489
INTERNATIONAL CLASSIFICATION		424	490						
A 61K 9/14									
A 61K 9/16									
A 61K 9/20									
A 61K 9/22									
A 61K 9/27									

S.Tran 01/28/04
(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

JAMES M. SPEAR
PRIMARY EXAMINER
James M. Spear
(Primary Examiner) (Date)
AU 1615 2-06-04

Total Claims Allowed: 21

O.G. Print Claim(s)	O.G. Print Fig.
1	1

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	18	31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
2	4		34		64		94		124		154		184
3	5	19	35		65		95		125		155		185
	6	20	36		66		96		126		156		186
4	7	21	37		67		97		127		157		187
5	8		38		68		98		128		158		188
6	9		39		69		99		129		159		189
7	10		40		70		100		130		160		190
8	11		41		71		101		131		161		191
	12		42		72		102		132		162		192
	13		43		73		103		133		163		193
9	14		44		74		104		134		164		194
10	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
	17		47		77		107		137		167		197
11	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21		51		81		111		141		171		201
12	22		52		82		112		142		172		202
	23		53		83		113		143		173		203
	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
13	26		56		86		116		146		176		206
14	27		57		87		117		147		177		207
15	28		58		88		118		148		178		208
16	29		59		89		119		149		179		209
17	30		60		90		120		150		180		210

Index of Claims

Application No.	Applicant(s)	
09/705,625	CHENG ET AL.	
Examiner	**Art Unit**	
Susan T. Tran	1615	

√	Rejected	–	(Through num ral) Cancelled	N	Non-El ct d	A	App al
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	1/28/04
	1	=
	2	
	3	
	4	=
	5	=
	6	
	7	=
	8	=
	9	=
	10	=
	11	=
	12	
	13	
	14	=
	15	=
	16	
	17	
	18	=
	19	
	20	
	21	
	22	=
	23	
	24	
	25	
	26	=
	27	=
	28	=
	29	=
	30	=
	31	=
	32	
	33	
	34	
	35	=
	36	=
	37	=
	38	
	39	
	40	
	41	
	42	
	43	
	44	
	45	
	46	
	47	
	48	
	49	
	50	

Claim		Date
Final	Original	
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

Claim		Date
Final	Original	
	101	
	102	
	103	
	104	
	105	
	106	
	107	
	108	
	109	
	110	
	111	
	112	
	113	
	114	
	115	
	116	
	117	
	118	
	119	
	120	
	121	
	122	
	123	
	124	
	125	
	126	
	127	
	128	
	129	
	130	
	131	
	132	
	133	
	134	
	135	
	136	
	137	
	138	
	139	
	140	
	141	
	142	
	143	
	144	
	145	
	146	
	147	
	148	
	149	
	150	

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

February 28, 2003

S i r:

In accordance with Applicant's duty of disclosure under 37 C.F.R.§1.56 and the provisions of 37 C.F.R. §§ 1.97 and 1.98, Applicants hereby make of record the documents listed on the accompanying Form PTO-1449 for consideration by the Examiner in connection with the examination of the above-identified patent application.

Applicants note that reference AM is being submitted in an envelope labeled "PROPRIETARY MATERIAL NOT OPEN TO PUBLIC. TO BE OPENED ONLY BY EXAMINER OR OTHER AUTHORIZED U.S. PATENT AND TRADEMARK OFFICE EMPLOYEE." as this material in the envelope is considered proprietary and is being submitted for consideration under MPEP §724 (8th Edition).

The biostudy (which resulted in the data submitted as reference AM) was performed using formulations prepared in accordance with U.S. Patent No. 6,099,859. 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 (*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.

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 fee is due, the Examiner is authorized to charge said fee to Attorney Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1012	SERIAL NO.: 09/705,625
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Xiu Xiu CHENG, et al.	
		FILING DATE: November 3, 2000	GROUP: 1615

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	6 4 7 5 5 2 1	11/05/2002	Timmins et al.	424	469	Sep. 16, 1999
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AH							
	AI							
	AJ							
	AK							
	AL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AM	Andrx Pilot Biostudy Data (20 pages)
	AN	
	AO	
	AP	
	AQ	
	AR	
	AS	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: To Be Assigned	Art Unit: 1614
Re: Application of:	Chih-Ming CHEN, et al.
Serial No.:	09/705,625
Filed:	November 3, 2000
For:	**METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

September 17, 2001

S i r:

In accordance with Applicant's duty of disclosure under 37 C.F.R.§1.56 and the provisions of 37 C.F.R. §§ 1.97 and 1.98, Applicants hereby make of record the documents listed on the accompanying PTO-1449 Form for consideration by the Examiner in connection with the examination of the above-identified patent application.

This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b) before the mailing of a first Office Action on the merits. Accordingly, it is believed that no fee is due.

I hereby certify that the documents referred to as attached therein and/or fee are being deposited with the United States Postal Service with sufficient postage as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on September 17, 2001.
DAVIDSON, DAVIDSON & KAPPEL, LLC
BY: _____

However, if it is determined that any fee is due, the Examiner is authorized to charge said fee to Attorney Deposit Account No. 50-0552.

It is respectfully requested that the references cited on the accompanying PTO Form-1449 be considered and made of record. If any of the publications listed thereon are missing, the Examiner is requested to contact the undersigned so that a copy can be promptly forwarded.

It is respectfully submitted that the pending claims are patentable over all the references made of record at this time.

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

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
300.1012	09/705,625
APPLICANTS: Chih-Ming CHEN, et al.	
FILING DATE: November 3, 2000	GROUP: 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	AA	6	0	1	0	7	1	8		1/4/00	Al-Razzak et al.	424	464	
	AB	5	8	5	8	3	9	8		1/12/99	Cho	424	450	
	AC	5	6	9	1	3	8	6		11/25/97	Inman et al.	514	691	
	AD	5	6	8	8	5	1	8		11/18/97	Ayer et al.	424	422	
	AE	5	6	7	4	9	0	0		10/7/97	Ubillas et al.	514	557	
	AF	5	6	6	8	1	1	7		9/16/97	Shapiro	514	55	
	AG	5	6	6	7	8	0	4		9/16/97	Wong et al.	424	472	
	AH	5	6	5	0	1	7	0		7/22/97	Wright et al.	424	473	
	AI	5	6	3	1	2	2	4		5/20/97	Efendic et al.	514	12	
	AJ	5	6	2	9	3	1	9		5/13/97	Luo et al.	514	284	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	AK	9	9	4	7	1	2	8		9/23/99	WO	A61K	9/24		
	AL	9	9	4	7	1	2	5		9/23/99	WO	A61K	9/20		
	AM	9	9	2	9	3	1	4		6/17/99	WO	A61K	31/155		
	AN	9	6	0	8	2	4	3		3/21/96	WO	A61K	31/155		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AO	*Physicians' Desk Reference* (54th Ed. 2000), pp. 831-835.
	AP	Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371.
	AQ	Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.
	AR	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.
	AS	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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1012	SERIAL NO. 09/705,625
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE November 3, 20000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	BA	5	6	1	4	5	7	8		3/25/97	Dong et al.	524	377	
	BB	5	5	9	1	4	5	4		1/7/97	Kuczynski et al.	424	486	
	BC	5	5	4	5	4	1	3		8/13/96	Kuczynski et al.	424	473	
	BD	5	5	4	3	1	5	6		8/6/96	Roorda et al.	424	484	
	BE	5	5	1	2	2	9	3		4/30/96	Landrau et al.	424	449	
	BF	5	4	1	3	5	7	2		5/9/95	Wong et al.	604	892.1	
	BG	5	3	0	8	3	4	8		5/3/94	Balaban et al.	604	892.1	
	BH	5	1	8	5	1	5	8		2/9/93	Ayer et al.	424	473	
	BI	5	1	7	8	8	6	7		1/12/93	Guittard et al.	424	473	
	BJ	5	1	4	1	7	5	2		8/25/92	Ayer et al.	424	473	
	BK	5	1	2	0	5	4	8		6/9/92	McClelland et al.	424	473	
	BL	5	1	1	0	5	9	7		5/5/92	Wong et al.	424	438	
	BM	5	0	9	1	1	9	0		2/25/92	Kuczynski et al.	424	473	
	BN	5	0	7	1	6	0	7		12/10/91	Ayer et al.	264	112	
	BO	5	0	2	4	8	4	3		6/18/91	Kuczynski et al.	514	255.06	
	BP	4	9	6	3	1	4	1		10/16/90	Eckenhoff	604	892.1	
	BQ	4	8	9	2	7	3	9		1/9/90	Shah et al.	424	473	
	BR	4	8	6	5	5	9	8		9/12/89	Eckenhoff	604	892.1	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	BS														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	BT	

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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1012	SERIAL NO. 09/705,625
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	CA	4	8	5	1	2	2	9		7/25/89	Magruder et al.	424	457	
	CB	4	7	8	3	3	3	7		11/8/88	Wong et al.	424	468	
	CC	4	7	7	7	0	4	9		10/11/88	Magruder et al.	424	457	
	CD	4	7	0	4	1	1	8		11/3/87	Eckenhoff	424	438	
	CE	4	6	9	2	3	3	6		9/8/87	Eckenhoff et al.	424	468	
	CF	4	6	2	7	8	5	0		12/9/86	Deters et al.	604	892.1	
	CG	4	6	2	4	8	4	7		11/25/86	Ayer et al.	424	467	
	CH	4	6	1	5	6	9	8		10/7/86	Guittard et al.	604	892.1	
	CI	4	6	1	2	0	0	8		9/16/86	Wong et al.	604	892.1	
	CJ	4	6	0	9	3	7	4		9/2/86	Ayer	424	473	
	CK	4	5	8	7	1	1	7		5/6/86	Edgren et al.	424	473	
	CL	4	5	2	2	6	2	5		6/11/85	Edgren	424	473	
	CM	4	1	1	1	2	0	1		9/5/78	Theeuwes	424	473	
	CN	4	0	8	8	8	6	4		5/9/78	Theeuwes et al.	219	121.71	
	CO	4	0	8	0	4	7	2		3/21/78	Bohuon	514	555	
	CP	4	0	7	7	4	0	7		3/7/78	Theeuwes et al.	424	427	
	CQ	4	0	6	3	0	6	4		12/13/77	Saunders et al.	219	121.7	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	CR														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	CS	

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.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1012	SERIAL NO. 09/705,625
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	DA	4	0	3	6	2	2	8		7/19/77	Theeuwes	424	473	
	DB	4	0	3	4	7	5	8		7/12/77	Theeuwes	424	427	
	DC	4	0	0	8	7	1	9		2/22/77	Theeuwes et al.	424	427	
	DD	3	9	5	7	8	5	3		5/18/76	Bohuon	560	143	
	DE	3	9	5	2	7	4	1		4/27/76	Baker	424	405	
	DF	3	9	1	6	8	9	9		11/4/75	Theeuwes et al.	424	424	
	DG	3	8	4	5	7	7	0		11/5/74	Theeuwes et al.	424	427	
	DH													
	DI													
	DJ													
	DK													
	DL													
	DM													
	DN													
	DO													
	DP													
	DQ													

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	DR														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	DS	

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.

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Page	Art Unit: 1615

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

November 25, 2003

Communication accompanying the

Statement of Substance of Interview Under 37 CFR §1.133

S i r:

Upon review of the prosecution history of the present application during the preparation of this response, it was noted that complete copies of the PTO-1449 forms submitted with the Information Disclosure Statements of September 17, 2001 and February 28, 2003 were not initialed and returned to the undersigned. As certain references were disassociated from the file, Applicants again include herewith the Information Disclosure Statements of September 17, 2001 and February 28, 2003, along with the PTO-1449 forms and the references cited therein. The Examiner is requested to consider all of the references herein and return the initialed PTO-1449 forms to the undersigned.

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.

An early and favorable action is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Page	Art Unit: 1615

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

November 25, 2003

Statement of Substance of Interview Under 37 CFR §1.133

S i r:

Reconsideration of the present application in view of the following remarks is respectfully requested.

I. INTRODUCTORY COMMENTS

The undersigned gratefully acknowledges the courtesies extended by Examiner Page to the undersigned and Ted Whitlock, Esq. during the Interview conducted at the USPTO on November 20, 2003.

The Interview conducted on November 20, 2003 also included a separate discussion of applicant's copending Application Serial No. 09/705,630. A separate Amendment Under 37 CFR§1.111 and Statement of Substance of Interview Under 37 CFR §1.133 have been submitted for Serial No. 09/705,630.

II. REMARKS

During the Interview, the undersigned discussed the Office Action dated July 14, 2003 and applicants' response dated October 14, 2003.

In that Office Action, the Examiner had indicated that claim 25 would be allowable if rewritten in independent form. By virtue of the amendment the subject matter of claim 25 was rewritten in independent form, without prejudice to applicants pursuing remaining subject matter in continuation applications.

It was agreed that the claims were allowable over the prior art previously relied upon by the Examiner.

Nevertheless, during the course of the interview, the rejection of claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) over Lewis et al. in combination with Chiao and Drug Facts and Comparisons or Moeckel et al. in combination with Chiao and Drug Facts and Comparisons; and claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) over Cheng et al. in view of Drug Facts and Comparisons, was discussed.

During the interview, it was pointed out to Supervisory Examiner Page that Lewis et al. is directed to a combination product (insulin sensitizer plus another antidiabetes agent, which could be metformin), wherein it is stated that one or both of the active agents could be in modified release form. It was noted that Lewis et al. provide no in-vivo data whatsoever, and in fact do not mention any possible pharmacokinetic parameters which their formulations should meet. As stated in the last Office Action, Lewis et al. "do not teach the exact release profile(s) of the instant claims." It was further argued that Chaio and Drug Facts and Comparisons do not overcome the deficiencies of Lewis et al. with respect to the particular T_{max} range set forth in the

claims. Supervisory Examiner Page agreed that the claimed T_{max} range was patentable over the combination of Lewis, Chiao and Drug Facts and Comparisons.

During the interview, it was pointed out to Supervisory Examiner Page that the Moeckel et al. reference, while directed to retarded tablets containing metformin, does not suggest that the formulations described therein are useful for once-a-day administration. Instead, Moeckel et al. state that the retarded tablets of their invention "release metformin in a controlled manner over a time period of 0.5 – 10 hours preferably over 4 hours (FIG. 1)." (Column 5, lines 30-32). It was noted that Moeckel et al. provide no in-vivo data whatsoever, and in fact do not mention any possible pharmacokinetic parameters which their formulations should meet. As stated in the last Office Action, Moeckel et al. "do not teach the exact release profile(s) of the instant claims." It was further argued that Chaio and Drug Facts and Comparisons do not overcome the deficiencies of Lewis et al. with respect to the particular T_{max} range set forth in the claims. In response, Supervisory Examiner Page agreed that the claimed T_{max} range was patentable over the combination of Moeckel, Chiao and Drug Facts and Comparisons.

During the Interview, with respect to the rejection based on the combination of Cheng, et al. and Drug Facts and Comparisons, the T_{max} data presented in the Cheng, et al. reference was discussed in detail, and the Examiner's attention was directed to the discussion provided in applicants' responsive papers of February 2003 with respect to the T_{max} information presented in the '859 patent. It was pointed out to Supervisory Examiner Page that the '859 patent was the U.S. priority application to the Cheng, et al. reference. The relationship of the claimed T_{max} range of claim 1 (5.5 – 7.5 hours) when the dosage forms of the invention are administered after dinner was discussed with respect to providing the highest level of the drug in the blood at night (e.g., when gluconeogenesis is greatest; see the specification at pages 13-14). Supervisory Examiner Page considered the closest prior art to teach a T_{max} of 8 hours (the Cheng, et al. reference).

Supervisory Examiner Page agreed that the "applicants' arguments regarding the Tmax are persuasive that the method claims distinguish over the prior art" and indicated that the claims of record are allowable. (See the Examiner Interview Summary Record of November 20, 2003).

During the Interview, the rejection of claims 1, 4-5, 7-15, and 18-31 for obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859; claims 1-39 of U.S. Patent No. 6,284,275; and claims 1-4 of U.S. Patent No. of U.S. Patent No. 6,099,862 were discussed. In addition the provisional rejection of claims 1, 4-5, 7-15, and 18-31 over claims 1-29 of copending Application No. 09/726,193 was discussed.

During the interview, the Examiner indicated that the above-mentioned obviousness-type double patenting rejections would not be maintained as per the policy of the USPTO and *In re Schneller*, 158 USPQ 210 (CCPA 1968).

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.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

FORM PTO-1083

Docket No.: 300.1012
Date: November 25, 2003

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

In re application: Xiu Xiu Cheng, et al.
Serial No.: 09/705,625
Filed: November 3, 2000
For: **Methods For Treating Diabetes Via Administration Of Controlled Release Metformin**

Sir:

Transmitted herewith is an **Statement of Substance of Interview** 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)	(Col. 2)		SMALL ENTITY		OR	LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE		RATE	FEE
TOTAL CLAIMS	* Minus** =	0		x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus*** =	0		x $ 42	$		x $ 84	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $140	$		+ $280	$
				TOTAL:	$	OR	TOTAL:	$

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[X] Also transmitted herewith are:
[ ] Petition for extension under 37 C.F.R. 1.136
[X] Other: **Communication and Copies of previously submitted Information Disclosure Statements of September 17, 2001 and February 28, 2003 including PTO-1449 forms, and References Cited therein.**

[ ] Check(s) in the amount of **$0.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[ ] Petition fee for 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.

Clifford M. Davidson, Reg. No. 32,728
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
November 25, 2003
DAVIDSON, DAVIDSON & KAPPEL, LLC
BY:

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/24 — A1

(11) International Publication Number: WO 99/47128

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/US99/05233

(22) International Filing Date: 10 March 1999 (10.03.99)

(30) Priority Data:
09/044,446 19 March 1998 (19.03.98) US

(71) Applicant: BRISTOL–MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543–4000 (US).

(72) Inventors: TIMMINS, Peter; 5 Heathbank Avenue, Irby, Merseyside L61 4XD (GB). DENNIS, Andrew, B.; 7 Pear Tree Close, Barnston, Merseyside L60 1YD (GB). VYAS, Kiren, A.; 34 Adisham Green, Sittingbourne, Kent ME10 2SR (GB).

(74) Agents: RODNEY, Burton et al.; Bristol–Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543–4000 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD

(57) Abstract

A biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic metformin HCl salt, is provided which provides a dosage form that has prolonged gastric residence and includes (1) an inner solid particulate phase formed of substantially uniform granules containing a pharmaceutical having a high water solubility, and one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, and (2) an outer solid continuous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout, the outer solid continuous phase including one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, which may be compressed into tablets or filled into capsules. Methods for forming the so–described biphasic controlled release delivery system and using such biphasic controlled release delivery system for treating diabetes are also provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD

Field of the Invention

The present invention relates to a new dosage form for highly water soluble medicaments, such as the antidiabetic metformin, which provides for extended release of the drug and also for prolonged gastric residence which enables efficient delivery of drugs normally absorbed in the upper gastrointestinal tract, and to a method for preparing such dosage form.

Background of the Invention

Metformin is an antihyperglycemic agent of the biguanide class used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It is usually marketed in the form of its hydrochloride salt as Glucophage® (TM-BMS).

Metformin hydrochloride has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. Its oral bioavailability is in the range of 40 to 60% decreasing with increasing dosage which suggests some kind of saturable absorption process, or permeability/transit time limited absorption. It also has a very high water solubility (>300 mg/ml at 25°C). This can lead to difficulty in providing a slow release rate from a formulation and problems in controlling the initial burst of drug from such a formulation. These two difficulties are further compounded by the high unit dose, 500 mg per tablet, usually required for metformin hydrochloride (1997-PDR).

Drugs that have absorption limited to the upper gastrointestinal tract coupled with poor absorption in the distal small intestine, large intestine and colon are usually regarded as inappropriate candidates for

formulation into oral controlled delivery systems. This limitation on absorption (for example, in the upper gastrointestinal tract) is referred to as the "absorption window".

The gastrointestinal tract functions to propel ingested material from the stomach (where digestion takes place) into the small intestine (where absorption principally occurs) and on to the large intestine (where water is absorbed/secreted as part of body fluid regulation processes). Residence time for non-digestible materials in the stomach depends on whether one is dealing with a fed or a fasted subject. Typical gastric emptying times for particulate material (greater than a few millimeters in diameter) varies from a few tens of minutes in the fasted state to a few hours in the fed state. Transit times through the small intestine are consistently of the order of 3 to 4 hours.

Oral controlled release delivery systems function by releasing their payload of drug over an extended period of time following administration. Thus, controlled release dosage forms may only spend a relatively short period in the regions of the gastrointestinal tract where good absorption of certain drugs can occur. The dosage form will pass on to regions of the intestine where absorption of certain drugs is poor or non-existent, still releasing its contained drug albeit with a significant percentage of its payload still to be delivered. Drug when released from the dosage form in the circumstances described will not be absorbed. Thus, administration of a drug subject to a window of absorption in a conventional controlled release delivery system can lead to subtherapeutic blood levels and ineffective treatment of the disease state for which the drug was intended.

Drugs with very high solubility in water (for example, greater than 100 mg/ml) can be difficult to formulate into a controlled release oral dosage form. Solubility is a driving force for a drug substance to

dissolve in water; the greater the solubility the greater the rate of dissolution when all other factors are maintained constant.

In a controlled release dosage form, the formulator tries to reduce the rate of dissolution by, for example, embedding the drug in a polymeric matrix or surrounding it with a polymeric barrier membrane through which drug must diffuse to be released for absorption. To reduce the rate of release of drug from the dosage form to an appropriate level consistent with the blood level profile desired for a drug possessing very high water solubility, very large amounts of polymer would be required for the matrix or barrier membrane. If the total daily dose of drug to be delivered is of the order of only a few milligrams this may be feasible, but many drugs having the solubility properties described require total daily doses of the order of many hundreds of milligrams. Whilst it is possible to create oral controlled release dosage forms for such products by use of large amounts of polymer, an unacceptably large dosage form may result.

A further problem with highly water soluble drugs formulated into a controlled release dosage form is that a significant and variable "burst" of drug can occur from these systems. The burst of highly water soluble drug is the initial rapid release of drug that occurs from oral controlled release dosage forms when first contacting fluid, such as gastric fluids, prior to release controlling mechanisms of the dosage form establishing themselves and a stable release rate being provided. Hydration of any polymer matrix used to formulate the dosage form is a pre-requirement of establishing a stable release rate. Thus, a readily hydrating polymer is required to establish the desired stable release rate. However, if the polymer used is slow to hydrate, then an undesireable variable burst can occur.

Studies by Vidon et al (1) strongly suggest that there is permeability limited absorption of metformin.

Perfusing drug into the jejunum via an intubation technique showed a 2.5 fold greater area under the plasma concentration-time profile (a measure of the quantity of drug absorbed) compared with similar introduction of drug into the ileum. Drug was not detectable in plasma when drug was perfused into the colon. Drug will transit down the small intestine following dissolution from an ingested dosage form and, if absorption rate is slow, it is possible that drug can reach regions of poor permeability before absorption of a given dose is complete. In such a case, increasing the given dose may be predicted to result in a reduction in the percentage of administered dose absorbed.

Improvements in the therapeutic regimes employing metformin might be achieved by a dosage form that allows a reduction in dosing frequency, providing patient convenience that would probably improve compliance. Conventional extended release formulations have been demonstrated to invariably compromise the availability of metformin (2). This is probably because the dosage form carries a significant proportion of the drug content remaining to be released, as the dosage form is carried to regions of the gastrointestinal tract with very poor permeability to the drug. To reduce dosing frequency, the rate of release from the dosage form must be such as to extend effective plasma levels, but the potential for effective delivery at this rate is compromised by the combined influences of the significant reduction in permeability to the drug in passing from the proximal small intestine down to the colon and the limited residence time in the regions of the gastrointestinal tract where the drug is well absorbed. That transit time down the "useful" region of the gastrointestinal tract is only likely to be of the order of a few hours.

Maintained or even improved bioavailability from an extended release dosage form that releases metformin at a rate likely to provide the desired plasma levels of drug for an extended time period might, however, be possible

from a dosage form that has extended residence time in the upper gastrointestinal tract, resisting mechanisms that promote normal transit time for solid materials. That this principle might work in practice was demonstrated in an in-house study where metformin was co-administered with propantheline, an agent that reduces gastrointestinal motility. Compared with giving metformin alone, the combination provided an increased AUC, a delayed tmax and an extended time period over which therapeutically beneficial plasma levels of drug were maintained.

Giving a drug such as metformin for the treatment of diabetes with a further drug, such as propantheline, not used for the treatment of diabetes and where the sole intent of using the second agent is to achieve extended residence time in the upper GI tract, has many disadvantages although it is likely to allow effective extended delivery of metformin to an optimal absorption site. The co-administered drug may have other undesirable pharmacological effects or side effects deleterious to the patients well being and detract from the improved quality of life offered by the treatment for their diabetes. Furthermore, it may be difficult or impossible to appropriately co-formulate the two agents due to chemical compatibility issues or solubility differences, the latter preventing the required release rate of agent influencing residence time in the upper GI tract. Thus, the patient could be required to take separate, multiple medications to achieve the desired effect. The timing of taking the two medications would be critical to effective delivery of the drug with the limited window of absorption and many patients may thus fail to take their medication correctly resulting in ineffective treatment of their diabetes.

Prior Art Gastro-Retentive Systems

It would be desirable to provide a dosage form that inherently has the property of extended gastric residence, possessing some resistance to the pattern of waves of

motility present in the gastrointestinal tract that serve to propel material through it. There have been many attempts to provide for this, with varying degrees of success.

Possible approaches described in prior art include:

(1) Floating or buoyant systems:
These are designed to have a low density and thus should float on gastric contents after administration until the system either disintegrates (and presumably the resultant particles empty from the stomach) or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

(2) Bioadhesive systems:
These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened for example by continuing hydration of the outer layer of the device or by the persistent application of shear.

(3) Swelling and expanding systems:
These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (for example, less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet). On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree.

Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach.

Re: (1) Buoyant/floating systems

Buoyant systems designed to float on the gastric contents have been designed where buoyancy is created by low density of the formulation components. For example, Watanabe et al (3) used low density shells such as spherical polystyrene foam particles in which polymer and drug layers were loaded. Such a system has the required low density and will not need to disintegrate into small pieces to empty from the stomach, but may not have a controlled loss of density alternatively required for it to eventually exit from the stomach. It also has limited capacity for loading with drug in the thin layers that can be applied around the polystyrene shells. It would be difficult to also layer large amounts of polymer on such a system to retard the release of very water soluble drugs.

Sheth described hydrodynamically balanced systems including both capsules and tablets (4,5,6) which had low density to enable floating on the stomach contents and which slowly eroded after administration, losing buoyancy and being expelled from the stomach.

Buoyancy can also be combined with control of drug release at different pH values to make for a device with better control in case of drugs with very marked dependency of solubility on pH (7); hence dissolution of contained drug depending on environment pH.

These approaches may be applicable to many drugs dosed in doses of up to a maximum of a few hundred milligrams per day but may not be applicable to similar or higher dose levels of highly water soluble drugs. Where large amounts of polymer are needed to retard drug release as in the case of use of high water soluble drugs a capsule dosage form may not be possible on grounds of size. Furthermore, the relatively homogenous distribution of drug in the tablet versions of this technology would not readily

control the burst effect seen with a very water soluble drug.

A bilayer tablet approach (8) where the buoyancy generation comes from a separate layer to the drug containing layer having a release rate controlling property might overcome some of the problems seen with the hydrodynamically balanced systems, but this type of system would probably only be able to carry low drug payloads due to size constraints.

Approaches involving in situ gas generation within the system, where the gas is trapped within the dosage form on generation, encouraging buoyancy, might offer improved control over degree, onset time and persistence of buoyancy. Ichikawa (9) described such a device with a drug loaded core surrounded by the gas generating layer, which in turn was surrounded by a polymeric layer responsible for controlling drug release from the system.

Such floating or buoyant dosage forms seem to have met with limited clinical success due to the requirement that such dosage forms be taken with a suitable amount of fluid (normal gastric contents could be as little as a few tens of milliliters so that the total amount of fluid thus available would not be conducive to performance of such systems even when taken with a draught of water). Davis et al (10) found no benefit of floating formulations over non-floating formulations when studied in vivo. Their performance may also be posture dependent. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach (11). The physical size of such dosage forms seems to be as important if not more important as ability to float in encouraging prolonged gastric residence. Hence, floating/buoyant dosage forms might be expected to only have limited applications.

Re: (2) Bioadhesive systems

Polycarbophil has been identified as a suitable polymer for encouraging adhesion of orally administered dosage forms to the gastric mucosa, thereby prolonging residence time for a system designed to slowly deliver drug to absorptive sites in the proximal small intestine (Longer et al, J. Pharm. Sci., 74, 406-411 (1985)). The success seen in animal models with such systems has been found not to translate to human subjects due to differences in mucous amounts, consistency and turnover between animals and humans. Bioadhesive systems allow dosage forms to adhere to mucous, not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage forms would not appear to offer a solution for extended delivery of drug over a period of more than a few hours to the upper small intestine in humans.

Re: (3) Swelling/expanding systems

Other solutions to encouraging prolonged gastric residence have included dosage forms that unfold rapidly within the stomach to a size that resists gastric emptying. Such systems retain their integrity for an extended period and will not empty from the stomach at all until breakdown into small pieces occurs. Caldwell (12) describes a cross shaped device made of erodible polymer and loaded with drug which is folded and inserted into a hard gelatin capsule. Following oral administration the gelatin shell disintegrates and the folded device opens out. With a minimum size of 1.6cm and a maximum size of 5cm it will not pass from the stomach through the pylorus until the polymer erodes to the point where the system is sufficiently small that it can be passed from the stomach. Such a system may in fact obstruct the pylorus or even open earlier or later than intended possibly causing obstruction in the esophagus or small intestine. As such, it may represent a potential hazard to the patient.

An alternate approach to using size to modulate gastric residence of a dosage form is to use a hydrophilic erodible polymer system that is of a convenient size for administration to humans. On imbibing fluid the system swells over a short period of time to a size that will encourage prolonged gastric retention, allowing sustained delivery of contained drug to absorption sites in the upper gastrointestinal tract. Because these systems are made of an erodible and hydrophilic polymer or polymer mixture, they readily erode over a reasonable time period to pass from the stomach. The time period of expansion is such that this will not occur in the esophagus and if the system passes into the intestine in a partially swollen state, the erodibility and elastic nature of the hydrated polymer will eliminate the chance of intestinal obstruction by the device.

Mamajek et al, U.S. Patent No. 4,207,890, describes a system wherein a drug release rate controlling (metering) component and a swelling component are mixed with drug enclosed within a membrane. The swelling component draws in fluid through the membrane, which maintains system integrity during its functioning, and the drug metering component controls the rate of drug release through the membrane.

Urquart (13) describes a different approach which consists of a matrix of hydrogel that imbibes fluid to swell the system so that it reaches a size encouraging prolonged gastric retention. This matrix surrounds a plurality of tiny pills consisting of drug with a release rate controlling wall of fatty acid and wax surrounding each of the pills.

Shell (14,15,16) has described systems for delivering drugs for the treatment of diseases of the upper gastrointestinal tract or for delivering drugs that might be irritating or injurious to the gastrointestinal mucosa. A swelling hydrogel polymer has embedded within it drug particles that dissolve once the hydrogel matrix is

hydrated. The swollen matrix is of a size to encourage gastric retention but only dissolved drug reaches the mucosa and this can be delivered in a sustained manner. Such a system thus does not insult the mucosa with solid particles of irritant drug and is suitable for delivering drug to upper gastrointestinal tract. These systems only apply in case of drugs of limited water solubility.

In the case of metformin, it is desirable to provide a dosage form that allows extended delivery of the drug and has a prolonged gastric residence via swelling of the system rather than unfolding or expanding of a folded device, and that may be manufactured on a commercial scale. The prolonged gastric residence time is required due to the window of absorption seen with metformin.

Another problem for extended delivery of metformin is its very high water solubility. High levels of polymer would be needed if many prior art approaches to provide the required release rate are employed. This could result in a rapid and variable initial release (burst) of drug from an extended release dosage form. The latter will thus give rise to difficulty in providing a true control of drug release and minimal inter-patient variability in drug plasma levels (arising from the possibility of variable burst of drug from tablets given to different patients).

Prior Art Controlled Release Systems for Very Soluble Drugs

Typical prior art techniques for creating a controlled release oral dosage form would involve either matrix systems or multi particulate systems. Matrix systems may be formulated by homogeneously mixing drug with hydrophilic polymers, such as hydroxypropylmethylcellulose, hydroxypropylcellulose, polyethylene oxide, carbomer, certain methacrylic acid derived polymers, sodium alginate, or mixtures of components selected from these, and compressing the resultant mixture into tablets (employing some other excipients where needed). Hydrophobic polymers,

such as ethyl cellulose, certain polymeric methacrylic acid esters, cellulose acetate butyrate, poly(ethylene-co-vinyl-acetate) may be uniformly incorporated with the above materials to give additional control of release. A further alternative involves embedding drug within a wax based tablet, by granulation or simply mixing of drug with a wax, such as carnauba wax, microcrystalline wax or commercially available purified fatty acid esters. As noted above, it may not be possible to use these approaches with very highly water soluble drugs.

Multi particulate systems consist of a dosage form based on a plurality of drug loaded spheres, prepared by layering drug onto a core, usually a sugar-starch mixture sphere of around 0.8mm diameter, until a sufficient level is reached, and then providing a drug release barrier around the drug-loaded sphere. Drug-loaded spheres can also be made by wet massing a mixture of drug and excipients, forcing the wet mass through a perforated screen to form short strands which are rounded in a spheronisation apparatus before drying and having the drug release barrier applied. The drug release barrier can be a wax, such as carnauba wax or glyceryl fatty acid esters, or a polymeric barrier, such as a mixture of ethyl cellulose and hydroxypropylmethylcellulose. These work well for moderately soluble drugs with doses in the units of milligrams to less than a few hundred milligrams per day.

In several examples, prior art systems seem to provide a controlled release formulation of a very water soluble drug by improving the multi particulate system approach. Fisher discloses a multi particulate system for highly soluble drugs especially opiate agonists (17) based on drug containing cores surrounded by a drug release controlling barrier which has the property of being partially soluble at a highly acidic pH.

Hansraj (18) coats drug loaded cores with methacrylic or acrylic acid derived polymers whose properties are modified by inclusion of at least one

anionic surfactant. In such a system, drug release of highly water soluble drugs is controlled without having to resort to the use of thick coatings on the release rate controlling layer.

Rollet (19) achieves prolonged release of a drug from a multi particulate formulation based on fine particles of hydrophilic and hydrophobic silicas or silicates. Presumably, this system would function for drugs of high water solubility.

Multi particulate systems are usually filled into capsules to provide unit dose forms because of the damage caused to such particles in trying to compress them into tablets. Total dose contained in a single unit is constrained by the loading possible in a hard gelatin capsule of easily swallowable size and is usually not more than a few hundred milligrams.

Single unit controlled release systems applicable to highly water soluble drugs include the application of multiple layers around a dose form as described by Howard (20). Where coating is not employed, special mixtures of polymers or formation of a complex with the drug have been used. Macrae (21) uses mixtures of polyethylene oxide and hydroxypropylmethylcellulose with optional enteric polymers to produce a constant release rate for highly water soluble drugs. Belenduik (22) combines the highly water soluble drug with a hydrophilic polymer based on acrylic acid and disperses this in a hydrophobic matrix.

Variations of Alza osmotic systems have been described suitable for highly water soluble drugs such as venlafaxine hydrochloride (23). These systems need two layers, a drug layer and an osmotically driven displacement layer all surrounded by a water permeable/drug impermeable membrane with an exit passage in this membrane for the drug.

Granules of highly water soluble clavulanate were prepared (24) having to employ a barrier layer of a hydrophobic waxy material in order to provide for

controlled release of this material when co-formulated with controlled release amoxycillin trihydrate granules in capsule or compressed tablet.

Description of the Invention

In accordance with the present invention, a novel way has been found of formulating drug with high water solubility and a limited window of absorption such as metformin or a salt thereof which has a window of absorption in the upper gastrointestinal tract, to provide a dosage form that inherently has prolonged gastric residence. This is accomplished (a) without need for co-administration of a drug such as propantheline, and (b) without need for low density formulation or gas generation within the formulation, The formulation of the invention (a) achieves extended gastric residence by virtue of size but will degrade in vivo so as not to have potential for causing gastric or intestinal obstruction, and (b) controls drug release adequately where the initial burst of drug is under control. The formulations of the invention will provide for an extended release formulation of drug with minimal interpatient variability in pharmacokinetic parameters.

The invention is applicable to all drugs having high water solubility and a limited window of absorption.

The biphasic controlled release delivery system of the invention is a heterogeneous two phase system which includes (1) an inner solid particulate phase in the form of individual granules or particles containing (a) drug which has a high water solubility and a limited window of absorption (such as in the upper gastrointestinal tract), and (b) an extended release material formed of one or more hydrophilic polymers, and/or one or more hydrophobic polymers, and/or one or more other type hydrophobic compounds (such as one or more waxes, fatty alcohols and/or fatty acid esters), and (2) an outer solid continuous phase in which granules or particles of inner solid particulate

phase are dispersed and embedded, the outer solid continuous phase including an extended release material formed of one or more hydrophilic polymers, and/or one or more hydrophobic polymers, and/or one or more other type hydrophobic compounds (such as one or more waxes, fatty alcohols and/or fatty acid esters).

The biphasic controlled release formulation of the invention is particularly adapted for delivery of high water soluble drugs, such as metformin and pharmaceutically acceptable salts thereof, in controlled and extended manner without significant initial burst of drug, and wherein release of drug (liberated from the individual dispersed particles forming the inner solid particulate phase) is effectively controlled. Drug upon being released from the particles of the inner phase, in effect, migrates through the outer solid continuous phase and then is released from the formulation into the upper gastrointestinal tract to be available for absorption.

As indicated, the inner solid particulate phase will be formed of individual discrete particles or granules each of which contains drug and one or more polymeric materials and/or other hydrophobic-type materials. In effect, the components of the inner solid particulate phase are in particulate association without having a barrier layer around the individual particles or granules.

The outer solid continuous phase is preferably a continuous phase or matrix having the particles or granules including drug (forming the inner solid phase) dispersed throughout and embedded in the continuous outer solid phase.

In addition, in accordance with the present invention, a method for treating diabetes is provided wherein the biphasic controlled release formulation of the invention containing an antidiabetic pharmaceutical is administered to a patient in need of treatment. The antidiabetic pharmaceutical employed is a biguanide,

preferably metformin or a pharmaceutically acceptable salt thereof such as the hydrochloride, fumarate of succinate.

The term "extended release material" as present in the inner solid particulate phase and the outer solid continuous phase refers to one or more hydrophilic polymers and/or one or more hydrophobic polymers and/or one or more other type hydrophobic materials, such as, for example, one or more waxes, fatty alcohols and/or fatty acid esters. The "extended release material" present in the inner solid particulate phase may be the same as or different from the "extended release material" present in the outer solid continuous phase. However, it is preferred that the "extended release material" present in the inner solid particulate phase be different from the "extended release material" present in the outer solid continuous phase.

The term "high water solubility" or similar term when characterizing a drug, medicament or pharmaceutical for use in the formulation of the invention refers to a solubility in water at ambient temperature of at least about 50 mg/ml H_2O, preferably at least about 100 mg/ml H_2O or more, and more preferably greater than 150 mg/ml.

The term "limited window of absorption" or similar term when characterizing a drug, medicament or pharmaceutical for use in the formulation of the invention refers to an oral bioavailability of less than about 75%, usually less than about 60%, usually decreasing with increasing dose, and almost invariably having permeability/transit time limited absorption.

The biphasic controlled release system of the invention will include the inner solid particulate phase in a weight ratio to the outer solid continuous phase within the range from about 0.5:1 to about 4:1, preferably from about 0.8:1 to about 2:1.

The inner solid particulate phase will contain drug in an amount within the range from about 10 to about 98% by weight, preferably from about 15 to about 95% by weight, and hydrophilic polymers and/or hydrophobic polymers and/or

other hydrophobic material in an amount within the range from about 5 to about 95% by weight, preferably from about 7 to about 85% by weight, the above % being based on the weight of the inner solid particulate phase. Where mixtures are employed, the hydrophilic polymer will be employed in a weight ratio to hydrophobic polymer and/or other hydrophobic material within the range from about 0.05:1 to about 19:1, preferably from about 0.1:1 to about 10:1.

The particles or granules of the inner solid particulate phase will have a mean particle size within the range from about 30 μm to about 0.8 mm, and preferably from about 50 μm to about 0.5 mm.

The outer solid continuous phase may contain mixtures of hydrophilic polymer and hydrophobic polymer and/or other hydrophobic material in a weight ratio of hydrophilic polymer to hydrophobic polymer or other hydrophobic material within the range from about 200:1 to about 0.05:1, preferably from about 100:1 to about 0.1:1.

Hydrophilic polymers which may be employed in the inner solid particulate phase and/or outer solid continuous phase include, but are not limited to hydroxypropylmethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, carboxymethylcellulose calcium, ammonium alginate, sodium alginate, potassium alginate, calcium alginate, propylene glycol alginate, alginic acid, polyvinyl alcohol, povidone, carbomer, potassium pectate, potassium pectinate, and the like.

Hydrophobic polymers which may be employed in the inner solid particulate phase and/or outer solid continuous phase include, but are not limited to ethyl cellulose, hydroxyethylcellulose, ammonio methacrylate copolymer (Eudragit RL™ or Eudragit RS™), methacrylic acid copolymers (Eudragit L™ or Eudragit S™), methacrylic acid-acrylic acid ethyl ester copolymer (Eudragit L 100-5™), methacrylic acid esters neutral copolymer (Eudragit NE

30D™), dimethylaminoethylmethacrylate-methacrylic acid esters copolymer (Eudragit E 100™), vinyl methyl ether/maleic anhydride copolymers, their salts and esters (Gantrez™).

Other hydrophobic materials which may be employed in the inner solid particulate phase and/or outer solid continuous phase include, but are not limited to waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

Where hydrophilic polymers and/or hydrophobic polymers are used in the inner solid particulate phase and/or the outer solid continuous phase, such polymers can be ionic or non-ionic, preferably ionic for the inner solid particulate phase and preferably non-ionic for the outer solid continuous phase.

Preferred ionic polymers for use in the inner solid particulate phase include sodium alginate, carbomer (Carbopol™), calcium carboxymethylcellulose, or sodium carboxymethylcellulose, xanthan gum, methacrylic acid-acrylic acid ethyl ester copolymer, dimethylaminoethylmethacrylate-methacrylic acid esters copolymer, cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, hydroxypropylmethylcellulose trimellitate, and hydroxypropylmethylcellulose maleate, with sodium carboxymethylcellulose being particularly preferred.

Preferred non-ionic polymers for use in the outer solid continuous phase are those which assure rapid hydration of the outer solid continuous phase to minimize a variable and significant burst of drug, yet effectively control the release of drug being liberated from the discrete particles or granules forming the inner solid

particulate phase. The liberated drug will migrate through the non-ionic polymers forming the outer solid continuous phase before being released from the dosage form and being available for absorption. Preferred polymers for the outer solid phase with the appropriate hydration characteristics include hydroxypropylmethyl cellulose 2910 USP (hydroxypropylmethylcellulose with a methoxyl content of 19-24% and a hydroxypropyl content of 7-12%), viscosity grades ranging from about 4000 to about 100,000 cps and hydroxypropylmethylcellulose 2208 USP (hydroxypropyl-methylcellulose with a methoxyl content of 28-30% and a hydroxypropyl content of 7-12%), viscosity grades ranging from about 3 to about 150 cps, and microcrystalline cellulose. In particular preferred embodiments of the outer solid phase, the above preferred polymers are used in admixture in weight ratios of hydroxypropylmethylcellulose 2910 USP:hydroxypropylmethylcellulose 2208 USP within the range from about 25:1 to about 50:1, preferably from about 30:1 to about 40:1.

Preferred biphasic controlled extended release delivery systems in accordance with the present invention are as follows.

A. Inner Solid Particulate Phase	% by Weight of Inner Solid Particulate Phase
(1) Metformin HCl (or other salt such as succinate or fumarate)	55 to 98
(2) Polymer or Hydrophobic material: ethylcellulose or sodium carboxymethylcellulose or glyceryl monostearate	5 to 45

(Average Particle Size of granules forming inner solid particulate phase: 0.05 to 2.0 mm)

B. Outer Solid Continuous Phase	% by Weight of Outer Solid Continuous Phase
(1) Hydroxypropylmethyl-cellulose 2208USP (100,000 cps)	60 to 100
(2) Microcrystalline cellulose	0 to 30
(3) Hydroxypropylmethyl cellulose 2910 USP (5 cps)	1 to 30
Weight Ratio of Inner Solid Phase: Outer Solid Phase	0.5:1 to 1.5:1

C. Optional Ingredients	% by Weight of Outer Solid Continuous Phase
Lubricant - Mg Stearate	0.02 to 1

The preferred drug (having high water solubility) for use herein is metformin or pharmaceutically acceptable salts thereof, including the hydrochloride salt and dibasic salts such as metformin (2:1) fumarate and metformin (2:1) succinate as described in pending U.S. Application Serial No. (not yet available) filed December, 1997 (internal code LA19) which is incorporated herein by reference. Other biguanides may be used such as phenformin or buformin or pharmaceutically acceptable salts thereof.

Most preferred are the metformin hydrochloride salt, metformin (2:1) succinate salt, and metformin (2:1) fumarate salt.

Where desired, metformin or a salt thereof may be used in combination with another antihyperglycemic agent which may be administered orally in the same dosage form in accordance with the invention, a separate oral dosage form or by injection.

It is believed that the use of the metformin or salt thereof in combination with another anti-hyperglycemic agent produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater

than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antihyperglycemic agent may be an oral antihyperglycemic agent preferably a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide being preferred.

The metformin or salt thereof will be employed in a weight ratio to the sulfonyl urea in the range from about 300:1 to about 50:1, preferably from about 250:1 to about 75:1.

The oral antihyperglycemic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in a separate oral dosage form.

The metformin salt of the invention will be employed in a weight ratio to the glucosidase inhibitor within the range from about 300:1 to about 2:1, preferably from about 200:1 to about 25:1.

The metformin or salt thereof may be employed in combination with a thiazolidinedione oral anti-diabetic agent (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), zorglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016) Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer).

The metformin or salt thereof will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 75:1 to about 0.1:1, preferably from about 5:1 to about 0.5:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral anti-diabetic agent may be incorporated in a single tablet with the biphasic controlled release formulation of the invention as a separate rapidly dissolving layer.

The metformin or salt thereof may also be employed in combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be administered via injection, or by transdermal or buccal devices.

In addition, in accordance with the present invention a method is provided for treating hyperglycemia including Type II diabetes (NIDDM) and/or Type I diabetes (IDDM) wherein a therapeutically effective amount of the biphasic formulatin of the invention containing metformin or a salt thereof, optionally in combination with another antihyperglycemic agent, is administered to a patient in need of treatment.

Where present, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701

(TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The following additional type high water soluble drugs may be employed in the biphasic controlled release delivery system of the invention:

antihypertensives and antidepressants related to guanethidine (as disclosed in U.S. Patent No. 2,928,829) and related to guanoxyfen (as disclosed in BE612362);

antibiotics and viricides such as related to

amidinomycin (as disclosed in JP 21,418);

stallimycin (as disclosed in DE 1,039,198);

Arphamenine B (as disclosed in published European Patent Application 85/133550A2);

chitinovorin-A (as disclosed in published European Patent Application 85/150,378A2 and U.S. Patent No., 4,723,004);

streptomycin (as disclosed in U.S. Patent No. 2,868,779);

SB-59 (as disclosed in Justus Liebigs, Ann. Chem. (1973) 7, 1112-1140);

TAN-1057-A (as disclosed in U.S. Patent No. 4,971,965);

streptoniazid (as disclosed in J. Am. Chem. Soc. (1953) 75, 2261);

immunostimulants related to

ST-789 (as disclosed in published European Patent Application 88/260588);

peptide hydrolase inhibitors related to

nafamastat (as disclosed in U.S. Patent No. 4,454,338);

gabexate (as disclosed in U.S. Patent No. 3,751,447);

sepimostat (as disclosed in U.S. Patent Nos. 4,777,182 and 4,820,730);

Factor Xa inhibitors related to

DX-9065a (as disclosed in published European Patent Application 92/0540051);

anti-inflammatory agents related to paranyline as disclosed in U.S. Patent No. 2,877,269;

peptidyl aldehydes (as disclosed in WO94/13693);

antianaphylactics related to GMCHA-TBP (Batebulast) (as disclosed in U.S. Patent No. 4,465,851);

anti-ulcer agents related to

benexate (as disclosed in U.S. Patent No. 4,348,410);

deoxyspergualin (as disclosed in U.S. Patent Nos. 4,518,532, 4,658,058 and 4,983,328); and arginine.

Other water-soluble drugs suitable for use herein include peptides preferably have a molecular weight from about 100 to 10,000, more preferably from about 100 to about 6,000 and having from 2 to 35 amino acid moieties. Higher molecular weight peptides, even those with a molecular weight of above 10,000, up to about 50,000, may also be accommodated in biphasic formulations of the present invention.

Suitable small peptides have from about 2 to about 10, more preferably from about 2 to about 6 amino acid moieties. Preferred small peptides include the fibrinogen receptor antagonists (RGD containing peptides) which are tetrapeptides with an average molecular weight of about 600. These peptide antagonists are highly potent platelet aggregation inhibitors at plasma levels as low as 1 pmol/mL. Preferred fibrinogen antagonists include the peptide cyclo(S,S)-N^a-acetyl-Cys-(N^a-methyl)Arg-Gly-Asp-Pen-NH_2 (Ali et al, EP 0341915, whose disclosure is herein incorporated by reference) and the peptide cyclo(S,S)-(2-mercapto)benzoyl-(N^a-methyl)Arg-Gly-Asp-(2-mercapto)-phenylamide (EP 0423212, whose disclosure is herein incorporated by reference). Other fibrinogen antagonists useful in the present invention are those peptides disclosed by Pierschbacher et al, WO 89/05150 (US/88/04403); Marguerie, EP 0275748; Adams et al, U.S. 4,857,508; Zimmerman et al, U.S. 4,683,291; Nutt et al, EP 0410537, EP 0410539, EP 0410540, EP 0410541, EP 0410767, EP

0410833, EP 0422937 and EP 0422938; Ali et al, EP 0372486; Ohba et al, WO 90/02751 (PCT/JP89/00926); Klein et al, U.S. 4,952,562; Scarborough et al, WO 90/15620 (PCT/US90/03417); Ali et al, PCT/US90/06514 and PCT/US92/00999; the peptide-like compounds disclosed by Ali et al, EP 0381033 and EP 0384362; and the RGD peptide cyclo-N^a-acetyl-Cys-Asn-Dtc-Amf-Gly-Asp-Cys-OH (in which Dtc is 4,4'-dimethylthiazolidine-5-carboxylic acid and Amf is 4-aminomethylphenylalanine).

The RGD peptide may be usefully included in the formulation of the invention in an amount up to about 600 mg/g of the hydrophilic phase or from 0.1 to 60 mg/g of the formulation.

Other peptides useful in the present invention include, but are not limited to, other RGD containing peptides such as those disclosed by Momany, U.S. 4,411,890 and U.S. 4,410,513; Bowers et al, U.S. 4,880,778, U.S. 4,880,777, U.S. 4,839,344; and WO 89/10933 (PCT/US89/01829); the peptide Ala-His-D-Nal-Ala-Trp-D-Phe-Lys-NH_2 (in which Nal represents β-naphthylalanine) and the peptides disclosed by Momany, U.S. 4,228,158, U.S. 4,228,157, U.S. 4,228,156, U.S. 4,228,155, U.S. 4,226,857, U.S. 4,224,316, U.S. 4,223,021, U.S. 4,223,020, U.S. 4,223,019 and U.S. 4,410,512.

Other suitable peptides include hexapeptides such as the growth hormone releasing peptide (GHRP) His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, (Momany, U.S. 4,411,890, the disclosure of which is herein incorporated by reference in its entirety). This may usefully be included in an amount up to about 250 mg/g of the hydrophilic phase or from 0.1 to 25 mg/kg of the formulation.

Suitable larger polypeptides and proteins for use in the controlled release formulations of the present invention include insulin, calcitonin, elcatonin, calcitoningene related peptide and porcine somatostatin as well as analogs and homologs thereof. Other suitable larger polypeptides include those disclosed by

Pierschbacher et al, U.S. 4,589,881 (>30 residues); Bittle et al, U.S. 4,544,500 (20-30 residues); and Dimarchi et al, EP 0204480 (>34 residues).

Other type of compounds useful in the present invention include analogs or homologs of LHRH which display potent LH releasing activity or inhibit the activity of LHRH; analogs or homologs of HP5 which possesses hematopoetic activity; analogs or homologs of endothelin which possess hypotensive activity; analogs or homologs of enkephalin which have antinociceptive activity; analogs or homologs of chlorecystokinin; analogs or homologs of cyclosporin A which have immunosuppressive activity; analogs or homologs of atrial natriuretic factor; peptidergic antineoplastic agents; analogs or homologs of gastrin releasing peptide; analogs or homologs of somatostatin; gastrin antagonists; bradykinin antagonists; neurotensin antagonists; bombesin antagonists; oxytocin agonists and antagonists; vasopressin agonists and antagonists; hirudin analogs and homologs; analogs and homologs of the cytoprotective peptidecyclolinopeptide; alpha MSH analogs; analogs, and homologs of MSH releasing factor (Pro-Leu-Gly-NH_2); peptides which inhibit collagenase; peptides which inhibit elastase, peptides which inhibit renin; peptides which inhibit HIV protease; peptides which inhibit angiotensin converting enzyme; peptides which inhibit chymases and tryptases and peptides which inhibit blood coagulation enzymes.

Other suitable drugs include non-peptide therapeutic agents such as antibiotics, antimicrobial agents, antineoplastic agents, cardiovascular and renal agents, anti-inflammatory, immunosuppressive and immunostimulatory agents and CNS agents.

Preferably, the water-soluble drug is metformin or salt thereof as described above.

The biphasic controlled release formulation of the present invention can be administered to various mammalian

species, such as dogs, cats, humans, etc., in need of such treatment.

The biphasic controlled release system of the invention can be incorporated in a conventional systemic dosage form, such as a tablet or capsule. The above dosage forms may also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms of formulation containing metformin or salt thereof (whether by itself or with another antihyperglycemic agent) described above may be administered in amounts as described for metformin hydrochloride (Bristol-Myers Squibb Company's Glucophage®) as set out in the Physician's Desk Reference.

The combination of the metformin or salt thereof and the other antihyperglycemic agent may be formulated separately or, where possible, in a single formulation employing conventional formulation procedures.

The various formulations of the invention may optionally include one or more fillers or excipients in an amount within the range of from about 0 to about 90% by weight and preferably from about 1 to about 80% by weight such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium carbonate and/or cellulose derivatives such as wood cellulose and microcrystalline cellulose.

One or more binders may be present in addition to or in lieu of the fillers in an amount within the range of from about 0 to about 35% and preferably from about 0.5 to about 30% by weight of the composition. Examples of such binders which are suitable for use herein include polyvinylpyrrolidone (molecular weight ranging from about 5000 to about 80,000 and preferably about 40,000), lactose,

starches such as corn starch, modified corn starch, sugars, gum acacia and the like as well as a wax binder in finely powdered form (less than 500 microns) such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

Where the composition is to be in the form of a tablet, it will include one or more tableting lubricants in an amount within the range of from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition, such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax and the like. Other conventional ingredients which may optionally be present include preservatives, stabilizers, anti-adherents or silica flow conditioners or glidants, such as Syloid brand silicon dioxide as well as FD&C colors.

Tablets of the invention may also include a coating layer which may comprise from 0 to about 15% by weight of the tablet composition. The coating layer which is applied over the outer solid phase containing particles of inner solid phase embedded therein may comprise any conventional coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethylcellulose, and/or a hydrophobic polymer like methacrylic acid esters neutral polymer, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, β-pinene polymers, glyceryl esters of wood resins and the like and one or more plasticizers, such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil and the like. Both core tablets as well as coating formulations may contain aluminum lakes to provide color.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols like methyl alcohol, ethyl alcohol or isopropyl alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

Where a color is employed, the color will be applied together with the film former, plasticizer and solvent compositions.

It will be recognized by one of skill in the art that the amount of drug required for therapeutic effect on administration will, of course, vary with the agent chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. Furthermore, the optimal quantity and spacing of individual dosages of a drug will be determined by the nature and extent of the condition being treated, the form, route and site of administration, the particular patient being treated and that such optima can be determined by conventional techniques. It will also be appreciated that the optimal course of treatment, this is, the number of doses given, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

As indicated, the preferred highly water-soluble drug will be metformin or a salt thereof, which will be employed in a dosage range from about 2 to about 43 mg/kg, preferably about 3 to about 36 mg/kg and more preferably from about 4.5 to about 30 mg/kg (or from about 150 to about 3000 mg, preferably from about 250 to about 2500 mg) on a regimen in single or 2 to 4 divided daily doses.

The biphasic controlled release formulation of the invention may be prepared in accordance with the following method of the invention.

A mixture of medicament (preferably metformin HCl) and hydrophilic polymer and/or hydrophobic polymer and/or other hydrophobic material are dispersed/dissolved in a suitable solvent such as water or an inert organic solvent such as ethanol, isopropanol, acetone or dichloromethane or appropriate mixtures of two or more thereof, to produce a substantially uniform granulation. The granulation is dried and passed through a 0.5 to 2 mm aperture screen to break down agglomerates.

The resulting dry granules are blended with hydrophilic polymer and/or hydrophobic polymer and/or other hydrophobic material. The resulting mix usually with lubricant is pressed into tablets or filled into capsules.

The finished dosage form is either a compressed tablet or a hard gelatin capsule, preferably a tablet. The tablet may be optionally film coated. The total amount of drug per dosage unit would be such as to offer a dosage form of convenient size for patients, but following ingestion would remain (or swell to, by hydration of the polymers used in the fabrication of the tablet) a size that does not easily pass through the pylorus (15mm or greater) when taken with a meal. As the tablet swells up to approximately three times its dry size following hydration, drug loads of up to 750 mg are possible, dependent upon the actual characteristics of the individual drug. Gradual erosion of the polymers of the formulation over a period of up to 15 hours ensures that the dosage form does not produce a gastrointestinal obstruction.

Useful metformin formulations of the invention show the following drug release characteristic when tested in vitro.

Time (hours)	% released
1	28-39
2	43-57
3	53-70
5	70-88
7	80-98
10	>85

The following Examples represent preferred embodiments of the invention.

Example 1

Biphasic Metformin HCl Formulation

25g of ethylcellulose N10 NF was dissolved/ dispersed in 100 ml of 95% ethanol. This dispersion was gradually added to 500 g of metformin hydrochloride in a planetary mixer to produce a uniform damp granulation. The granulation was dried at 55°C for one hour and passed through a 0.8mm aperture screen to break down agglomerates. The metformin-ethylcellulose granules (541g) were blended with 351.5g of hydroxypropylmethylcellulose 2208 USP (100,000 cps grade), 10g of hydroxypropylmethylcellulose 2910 USP (5 cps grade) and 100.5g of microcrystalline cellulose in a planetary mixer for 10 minutes. Finally this mix was lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500mg metformin hydrochloride. When subjected to *in vitro* drug release testing, the following results were obtained.

Time (hours)	% metformin released
1	38.1
2	56.3
3	69.5
4	79.7
5	87.4
6	93.1
7	97.7
8	100

Example 2

Biphasic Metformin HCl Formulation

51g of sodium carboxymethylcellulose (Blanose 7HF) was mixed with 500g of metformin hydrochloride and granulated with 95% ethanol in a small planetary mixer. The damp granulation was passed through a 2mm aperture screen and then dried in an oven at 55°C for one hour. The dried granulation (530g) was blended with 344g of hydroxypropylmethylcellulose 2208 USP (100,000 cps grade),

9.5g of hydroxypropylmethylcellulose 2910 USP (5cps grade) and 100g of microcrystalline cellulose in a planetary mixer for 10 minutes. This blend was lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500mg metformin hydrochloride. When the tablets were subjected to in vitro release testing the following results were obtained.

Time (hours)	% metformin released
1	35.3
2	51.4
3	62.6
4	70.7
5	76.7
6	82.1
7	85.3
8	88.5
10	92.6

Example 3

Biphasic Metformin HCl Formulation

Metformin hydrochloride (502.5g) was mixed with sodium carboxymethylcellulose (Blanose 7HF) (50g) for five minutes in a small planetary mixer and sufficient purified water added with continued mixing to produce a damp granular mass. The wet granulation was dried at 60°C for 1 hour and then size reduced in a hammer mill. The granulation was dry blended with a mixture prepared from 385g of hydroxypropylmethylcellulose 2208 USP (100,000 cps grade), 10g of hydroxypropylmethylcellulose 2910 USP (5 cps grade) and 102g of microcrystalline cellulose in a planetary mixer for 10 minutes. Finally this mix was lubricated by mixing with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 0.5g of metformin hydrochloride. When tested for in vitro release of metformin the following results were obtained.

Time (hours)	% metformin released
1	33.1
2	47.6
3	57.5
4	65.1
6	76.5
8	84.3
10	88.6

Example 4

Biphasic Metformin HCl Formulation

200g of glycerol monostearate was heated to 70°C in a high shear mixer bowl and 199g of metformin hydrochloride was added and the mixer operated with impeller at 90 rpm and chopper at 215 rpm for 5 minutes. A further 796g of metformin hydrochloride was added gradually with continued mixing, maintaining the granulation at 70°C and with an increase in chopper speed first to 500 rpm for 13 minutes, then to 1000 rpm for a further 3 minutes. The bowl was then cooled to 60°C, the impeller speed was reduced to 20 rpm and the chopper speed increased to 2000 rpm. Cooling was continued with adjustment in impeller and chopper speed to eventually provide a cooled solid granulation. The cooled granulation was deagglomerated by passing through a 0.8mm screen.

540.5g of the granulation was blended with 350g of hydroxypropylmethylcellulose 2208 USP (100,000 cps grade), 10g hydroxypropylmethylcellulose 2910 USP (5 cps grade) and 100g of microcrystalline cellulose in a planetary mixer for 10 minutes. The blend was lubricated by blending with 1% w/w magnesium stearate and then compressed into capsule shaped tablets each containing 500mg metformin hydrochloride. When tested for in vitro release of metformin, the following results were obtained.

Time (hours)	% metformin released
1	32.4
2	45.7
3	55.8
4	63.7
5	70.3
6	75.7
8	83.3
10	88.6

Example 5

Biphasic Metformin HCl Formulation

Tablets containing 500 mg metformin hydrochloride prepared according to Example 3 or Glucophage brand metformin hydrochloride 500 mg tablets was dosed (2 x 500 mg tablets) to 24 patients immediately after dinner. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24 hours and analyzed for metformin. The mean plasma profile demonstrated useful modification of drug release in vivo relative to the immediate release formulation and with no impact on bioavailability in contrast to other metformin extended release formulations reported in the literature.

Interpatient variability in pharmacokinetic parameters was acceptable as illustrated by the mean parameters (%CV) given in the table below:

Formulation	Cmax (ng/ml)	AUC (inf) (ng.hr/ml)	Tmax*(hr)	%UR
Glucophase	1226(16)	10128(14)	3.5(1,5)	43.3(20)
Example 3	978(13)	10483(21)	5(4,8)	42.7(18)

*median (min., max.)

The new formulations of the invention thus represent a useful advance in the administration of metformin hydrochloride to human in the treatment of diabetes.

Example 6

Preparation of Metformin (2:1) Fumarate

Metformin base (8.71 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H_2O [5:1]. With stirring, a solution of fumaric acid (4.05 moles) in ethanol was added over a period of one hour under a nitrogen atmosphere at ambient temperature (~20°C). Crystallization began to occur immediately. After stirring the slurry for one hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to afford the metformin (2:1) fumarate salt as a free-flowing white crystalline solid in 72 M% yield and melting point of 247-249°C.

The resulting metformin (2:1) fumarate slat had a solubility in water (mg/ml) of 140, a hygroscopicity measured at 95% relative humidity/25°C of less than 7% moisture uptake at 6 hours, and a low compaction susceptibility.

The so-formed metformin salt is used to prepare a biphasic controlled release formulation employing the procedure of Example 3.

Example 7

Preparation of Metformin (2:1) Succinate

Metformin base (8.95 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H_2O [5:1]. With stirring, a solution of succinic acid (4.42 moles) in ethanol was added over one hour under a nitrogen atmosphere at ambient temperature (~20°). Crystallization of the salt commenced shortly after addition of the succinic acid solution. After stirring the slurry for an hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to form the metformin (2:1) succinate salt as a free flowing white crystalline solid in 89 M% yield and melting point of 246-247°C.

The resulting metformin (2:1) succinate salt had a solubility in water (mg/ml) of 95, a hygroscopicity measured at 95% relative humidity/25°C of less than 1% moisture uptake at 30 minutes, and a low compaction susceptibility.

The so-formed metformin salt is used to prepare a biphasic controlled release formulation employing the procedure of Example 3.

REFERENCES

1. Vidon, N., Chaussade, S., Noel, M., Franchisseur, C., Huchet, B., Bernier, J.J. (1988), Diabetes Research and Clinical Practice, 4, 223-239.

2. Pentikainen, P.J. (1986), International Journal of Clinical Pharmacology, Therapy and Toxicology, 24, 213-220.

3. Watanabe, S., Kayano, M., Ishino, Y., Miyao, K. (1976), U.S. Patent 3,976,764.

4. Sheth, P., Tossounian, J.L. (1979), U.S. Patent 4,140,755.

5. Sheth, P., Tossounian, J. L. (1978), U.S. Patent 4,126,672.

6. Sheth, P., Tossounian, J. L. (1979), U.S. Patetn 4,167,558.

7. Dennis, A.B., Lee, K., Timmins, P. (1992), U.S. Patent 5,169,638.

8. Franz, M.R., Oth, M.P. (1993), U.S. Patent 5,232,704.

9. Ishikawa, M., Miyaka, Y., Watanabe, S. (1989), U.S. Patent 4,844,905.

10. Davis, S.S., Stockwell, A.F., Taylor, J.J., Hardy, J.G., Whalley, D.R., Wilson, C.G., Bechgaard, H., Christensen, F.N. (1986) Pharm. Res., 3, 208-213.

11. Timmermans, J., Moes, A. (1994), J. Pharm. Sci., 83, 18-24.

12. Caldwell, L.J., Gardener, C.R., Cargill, R.C. (1988), U.S. Patent 4,767,627.

13. Urquart, J., Theeuwes, F. (1984), U.S. Patent 4,434,153.

14. Shell, J.W. (1990), U.S. Patent 5,007,790.

15. Shell, J.W. (1993), World Patent WO 9318755.

16. Shell, J.W. (1996), U.S. Patent 5,582,837.

17. Fisher, M.C., Morella, A.M. (1994), European Patent 609961.

18. Hansraj, B.R., Bashir, R.H. (1992), European Patent 502642.

19. Rollet, M. (1987), French Patent 2594693.

20. Howard, S.A., Kotwal, P.M. (1997) U.S. Patent 5,645,858.

21. Macrae, R.J., Smith J.S. (1997), World Patent WO 9718814.

22. Belenduik, G.W., McCarty, J.A., Rudnic, E.M. (1996), U.S. Patent 5,484,608.

23. Bhatti, G.K., Edgren, D.E., Hatamkhani, Z., Wong, P.S., Wong, P.S.L. (1994), World Patent WO 9427589.

24. Palepu, N.R., Venkatesh, G.M., (1997) European Patent 701436.

What is claimed is:

1. A pharmaceutical formulation comprising (1) an inner solid particulate phase, and (2) an outer solid continuous phase in which particles of the inner solid particulate phase are dispersed and embedded, the particles of the inner solid particulate phase comprising (a) a pharmaceutical having a high water solubility; and (b) an extended release material, and the outer solid continuous phase comprising an extended release material.

2. The pharmaceutical formulation as defined in Claim 1 which is a biphasic heterogeneous controlled release formulation which is designed to release pharmaceutical from the particles forming the inner solid particulate phase through the outer solid continuous phase into the upper gastrointestinal tract.

3. The pharmaceutical formulation as defined in Claim 1 wherein the pharmaceutical is a biguanide antidiabetic agent.

4. The pharmaceutical formulation as defined in Claim 3 wherein the biguanide is metformin or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical formulation as defined in Claim 4 wherein the pharmaceutical is metformin hydrochloride.

6. The pharmaceutical as defined in Claim 1 wherein the inner solid particulate phase is in the form of discrete individual particles or granules and the outer solid continuous phase is a substantially continuous matrix having individual particles forming the inner solid particulate phase embedded therein and dispersed throughout.

7. The pharmaceutical formulation as defined in Claim 1 wherein the pharmaceutical has a solubility in water of at least about 100 mg/ml and a limited window of absorption in the upper gastrointestinal tract.

8. The pharmaceutical formulation as defined in Claim 1 wherein the pharmaceutical present in the inner

solid particulate phase is metformin or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical formulation as defined in Claim 1 wherein the inner solid particulate phase is present in a weight ratio to the outer solid continuous phase within the range from about 0.5:1, to about 4:1.

10. The pharmaceutical formulation as defined in Claim 1 wherein the pharmaceutical is present in the inner solid particulate phase in an amount within the range from about 10 to about 98% by weight of the inner solid particulate phase.

11. The pharmaceutical formulation as defined in Claim 1 wherein the extended release material present in the inner solid particulate phase comprises one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more other type hydrophobic materials; and the extended release material in the outer solid continuous phase comprises one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more other type hydrophobic materials.

12. The pharmaceutical formulation as defined in Claim 11 wherein the extended release material present in the inner solid particulate phase comprises one or more ionic polymers and the extended release material present in the outer solid continuous phase comprises one or more non-ionic polymers.

13. The pharmaceutical formulation as defined in Claim 12 wherein the ionic polymer comprises sodium alginate, carbomer, calcium carboxymethylcellulose or sodium carboxymethylcellulose, and the non-ionic polymer comprises hydroxypropylmethylcellulose 2910 USP, viscosity grade ranging from about 4000 to about 100,000 cps and hydroxypropylmethyl cellulose 2208 USP viscosity grade ranging from about 3 to about 150 cps and/or microcrystalline collulose.

14. The pharmaceutical formulation as defined in Claim 1 wherein the inner solid particulate phase has a

mean particle size within the range from about 30 μm to about 0.8 mm.

15. The pharmaceutical formulation as defined in Claim 1 wherein the inner solid particulate phase comprises metformin, metformin hydrochloride, metformin succinate (2:1) salt or metformin fumarate (2:1) salt, and ethyl cellulose and/or sodium carboxymethyl cellulose and/or glycerylmonostearate and the outer solid continuous phase comprises hydroxypropylmethylcellulose 2208 USP (100,000 cps), and/or hydroxypropylmethylcellulose 2910 USP (5 cps) and/or microcrystalline cellulose.

16. The pharmaceutical formulation as defined in Claim 1 wherein the pharmaceutical is a combination of metformin or a pharmaceutically acceptable salt thereof and another antihyperglycemic agent.

17. A method for preparing a biphasic controlled release delivery system, which comprises forming an inner solid particulate phase comprising individual particles comprising a pharmaceutical having a high water solubility and an extended release material and mixing the individual particles forming the inner solid particulate phase with an outer solid continuous phase comprising an extended release material to thereby disperse and embed the individual particles forming the inner solid particulate phase in the outer solid continuous phase.

18. A biphasic controlled release delivery system formed by the method as defined in Claim 17.

19. A method for treating diabetes which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of the formulation as defined in Claim 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05233

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/24
US CL :424/457

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/472

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

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

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,645,858 A (KOTWAL ET AL.) 08 July 1997, see cols. 5-8.	1-19
Y	WO 96/08243 A1 (MOECKEL ET AL.) 21 March 1996, see entire disclosure.	1-19
Y	EP 0 609 961 A1 (MORELLA ET AL.) 10 August 1994, see examples and tables.	1-19

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
03 JUNE 1999	07 JUL 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer D. Laurence for PETER KULKOSKY aco
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

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

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20

A1

(11) International Publication Number: WO 99/47125

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/US99/06024

(22) International Filing Date: 19 March 1999 (19.03.99)

(30) Priority Data:
09/045,330 20 March 1998 (20.03.98) US

(71) Applicant: ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US).

(72) Inventors: CHENG, Xiu, Xiu; Apartment 506, 3150 W. Rolling Hills Circle, Davie, FL 33328 (US). CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). JAN, Steve; 512 N.W. 120th Drive, Coral Springs, FL 33071 (US). CHOU, Joseph; 5755 N.W. 54th Place, Coral Springs, FL 33067 (US).

(74) Agent: ENDRES, Martin, P.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

(57) Abstract

A controlled release antihyperglycemic tablet that does not contain an expanding polymer and comprising a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Larvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

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 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.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride has been limited to the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® product which is a commercially available product from Bristol-Myers Squibb Co. containing metformin HCl.

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 and a 25% lower AUC in plasma 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.

It is an object of the present invention to provide a controlled or sustained release formulation for 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 for 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 for an antihyperglycemic drug that can provide continuous and 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.

It is an additional object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels approximately 8-12 hours after administration.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

SUMMARY OF THE INVENTION

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 semipermeable membrane coating surrounding the core; and
(c) at least one passageway in the semipermeable membrane.

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 antihypoglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form will be administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and provide therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 1 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 2 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 2 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 3 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 3 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 4 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 1 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 5 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the

commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 6 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions.

FIG. 7 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after breakfast).

FIG. 8 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after dinner).

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.

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-bis(ß-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.

The core of the present invention which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption 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 semipermeable membrane, preferably a modified polymeric membrane to form the controlled release tablet of the invention. The semipermeable membrane is permeable to the passage of an external fluid such as water and biological fluids and is impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the semipermeable 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 semipermeable 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 semipermeable 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, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

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 semipermeable membrane to form paths in the

semipermeable membrane for the fluid to enter the core and dissolve the active ingredient.

The semipermeable membrane may also be formed with commonly known excipients such 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, weaken 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 Patents such as 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607.

Generally, the membrane coating around the core will comprise from about 1% to about 5% and preferably about 2% to about 3% based on the total weight of the core and coating.

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 semipermeable

membrane of the dosage form or it may be incorporated into the semipermeable membrane.

In a preferred embodiment the dosage form will have the following composition:

	Preferred	Most Preferred
CORE:		
drug	50-98%	75-95%
binder	0-40%	3-15%
absorption enhancer	0-20%	2-10%
COATING:		
semipermeable polymer	50-99%	75-95%
flux enhancer	0-40%	2-20%
plasticizer	0-25%	2-15%

The dosage forms prepared according to the present invention should 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	0-25%	0-15%
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.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I	Core	
	metformin HCl	90.54%
	povidone[1], USP	4.38%
	sodium tribasic phosphate	4.58%
	magnesium stearate	0.5 %

[1]approximate molecular weight = 50,000; dynamic viscosity (10%w/v solution at 20°C) = 5.5-8.5 m Pa s.

(a) Granulation

The metformin HCl is delumped by passing it through a 40 mesh screen and collecting it in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying the binding solution of povidone and sodium tribasic phosphate 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 (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(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, 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 spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	
cellulose acetate (398-10)[2]	85%
triacetin	5%
PEG 400	10%

[2]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

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 clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	9	12
4	27	32
8	62	82
12	82	100

	88	105
16	92	108
20		

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 1.

Figure 4 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example. Also shown in Figure 4 is the in vivo metformin plasma profile of GLUCOPHAGE®, a commercially available pharmaceutical product containing the drug metformin HCl.

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I Core	
metformin HCl	88.555%
povidone[3], USP	6.368%
sodium lauryl sulfate	4.577%
magnesium stearate	0.5 %

[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-90F, 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 coated granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(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 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 spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	
cellulose acetate (398-10)[4]	85%
triacetin	5%
PEG 400	10%

[4]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

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 clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	12
4	29	27
8	55	52
12	72	71
16	81	83
20	87	91

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 2.

Figure 5 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example under fasting conditions. Figure 5 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fasting conditions.

Figure 6 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example

under fed conditions. Figure 6 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fed conditions.

Figures 5 and 6 clearly show that the dosage forms prepared in accordance with the present invention exhibit consistent bioavailability under both fed and fasting conditions while the GLUOPHAGE® product's bioavailability decreases in the presence of food.

EXAMPLE 3

A controlled release tablet containing 850 mg of metformin HCl and having the same formula as in Example 2 is prepared as described in Example 2 except that an additional hole was drilled on the plain side of the coated tablet. The additional hole had a diameter of approximately 1 mm.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	14
4	27	28
8	50	63
12	67	84
16	84	95
20	97	102

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 3.

Figure 7 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after breakfast. Figure 7 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after breakfast.

Figure 8 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after dinner. Figure 8 also

shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after dinner.

Table 1 is a summary of the bioavailability comparision data, test/reference ratio, shown in Figures 4-8 wherein the GLUCOPHAGE® product is the reference product in a two way crossover biostudy with n = 6.

TABLE 1

Formula	Figure	Study	AUC	Cmax	Tmax
Ex. 1	4	Fasting	0.202	0.12	2.15
Ex. 2	5	Fasting	0.369	0.214	1.73
Ex. 2	6	Fed (bkft)	0.628	0.305	1.94
Ex. 3	7	Fed (bkft)	0.797	0.528	1.82
Ex. 3	8	Fed (dinner)	0.850	0.751	2.00

bkft = breakfast

The results reported in Table 1 and Figures 4-8 show that dosage forms prepared in accordance with the present invention exhibit an increase in the bioavailability of the antihyperglycemic drug in the presence of food, especially when taken with or shortly after the evening meal.

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.

We claim:

1. A controlled release pharmaceutical tablet comprising:

(a) a core comprising:

(i) an antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer; and

(b) a semipermeable membrane coating covering said core; and

(c) at least one passageway in the semipermeable membrane.

2. A controlled release pharmaceutical tablet as defined in claim 1 wherein the antihyperglycemic drug is a biguanide.

3. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is metformin or a pharmaceutically acceptable salt thereof.

4. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is buformin or a pharmaceutically acceptable salt thereof.

5. A controlled release pharmaceutical tablet as defined in claim 1 wherein the binding agent is water soluble.

6. A controlled release pharmaceutical tablet as defined in claim 1 wherein the water soluble binding agent is polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, waxes or mixtures thereof.

7. A controlled release pharmaceutical tablet as defined in claim 6 wherein the water soluble binding agent is polyvinyl pyrrolidone.

8. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is selected from

the group consisting of fatty acids, surfactants, chelating agents, bile salts or mixtures thereof.

9. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a fatty acid selected from the group consisting of capric acid, oleic acid or their monoglycerides.

10. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a surfactant selected from the group consisting of sodium lauryl sulfate, sodium taurocholate and polysorbate 80.

11. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a chelating agent selected from the group consisting of citric acid, phytic acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(ß-aminoethyl ether)-N,N,N,N-tetraacetic acid.

12. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a bile salt.

13. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is sodium lauryl sulfate.

14. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane around the core is a water insoluble cellulose derivative.

15. A controlled release pharmaceutical tablet as defined in claim 14 wherein the water insoluble cellulose derivative in the membrane around the core is cellulose acetate.

16. A controlled release pharmaceutical tablet as defined in claim 1 wherein semipermeable membrane comprises a flux enhancer.

17. A controlled release pharmaceutical tablet as defined in claim 16 wherein the flux enhancer is sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers or mixtures thereof.

18. A controlled release pharmaceutical tablet as defined in claim 17 wherein the flux enhancer is polyethylene glycol with an average molecular weight between 380 and 420.

19. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane comprises a plasticizer.

20. A controlled release pharmaceutical tablet as defined in claim 19 wherein the plasticizer is triacetin.

21. A controlled release pharmaceutical tablet as defined in claim 1 wherein at least two passageways are formed in the semipermeable membrane.

22. A controlled release pharmaceutical tablet as defined in claim 1 wherein the peak plasma level is obtained 8-12 hours after administration.

23. A controlled release pharmaceutical tablet as defined in claim 1 further comprising an effective amount of the antihyperglycemic drug coated onto the semipermeable membrane or mixed into the semipermeable membrane to

provide an immediate release of an effective amount of the antihyperglycemic drug.

24. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:
50-98% of the drug;
0-40% of the binding agent; and
0-20% of the absorption enhancer; and the coating comprises:
50-99% of the polymer;
0-40% of the flux enhancer; and
0-25% of the plasticizer.

25. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:
75-95% of the drug;
3-15% of the binding agent; and
2-10% of the absorption enhancer; and the coating comprises:
75-95% of the polymer;
2-20% of the flux enhancer; and
2-15% of the plasticizer.

26. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile 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:
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 not less than 50% of the drug is released;
after 16 hours not less than 60% of the drug is released;
and after 20 hours not less than 70% of the drug is released.

27. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile 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:
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 not less than 60% of the drug is released;
after 16 hours not less than 70% of the drug is released;
and after 20 hours not less than 80% of the drug is released.

28. A controlled release pharmaceutical tablet as defined in claim 1 that is administered with or shortly after the evening meal.

29. A controlled release antihyperglycemic tablet comprising:
(a) a core consisting essentially of:
(i) metformin or a pharmaceutically acceptable salt thereof;
(ii) a water soluble binding agent; and
(iii) an absorption enhancer; and
(b) a semipermeable membrane coating covering said core comprising:
(i) cellulose acetate;
(ii) a flux enhancer; and
(iii) a plasticizer; and
(c) at least one passageway in the semipermeable membrane.

30. A controlled release pharmaceutical tablet as defined in claim 29 wherein the peak plasma level is obtained 8-12 hours after administration.

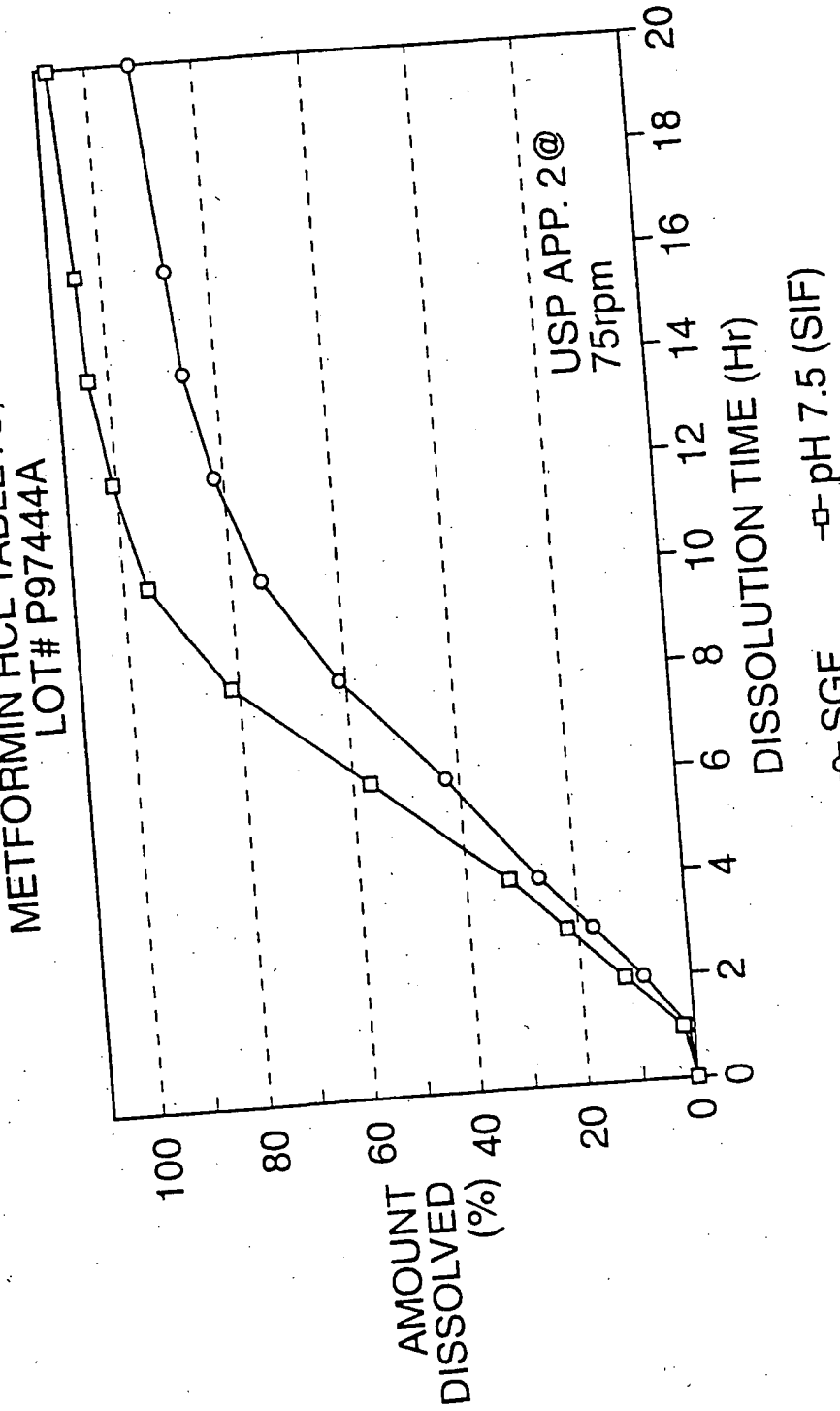


FIG. 1

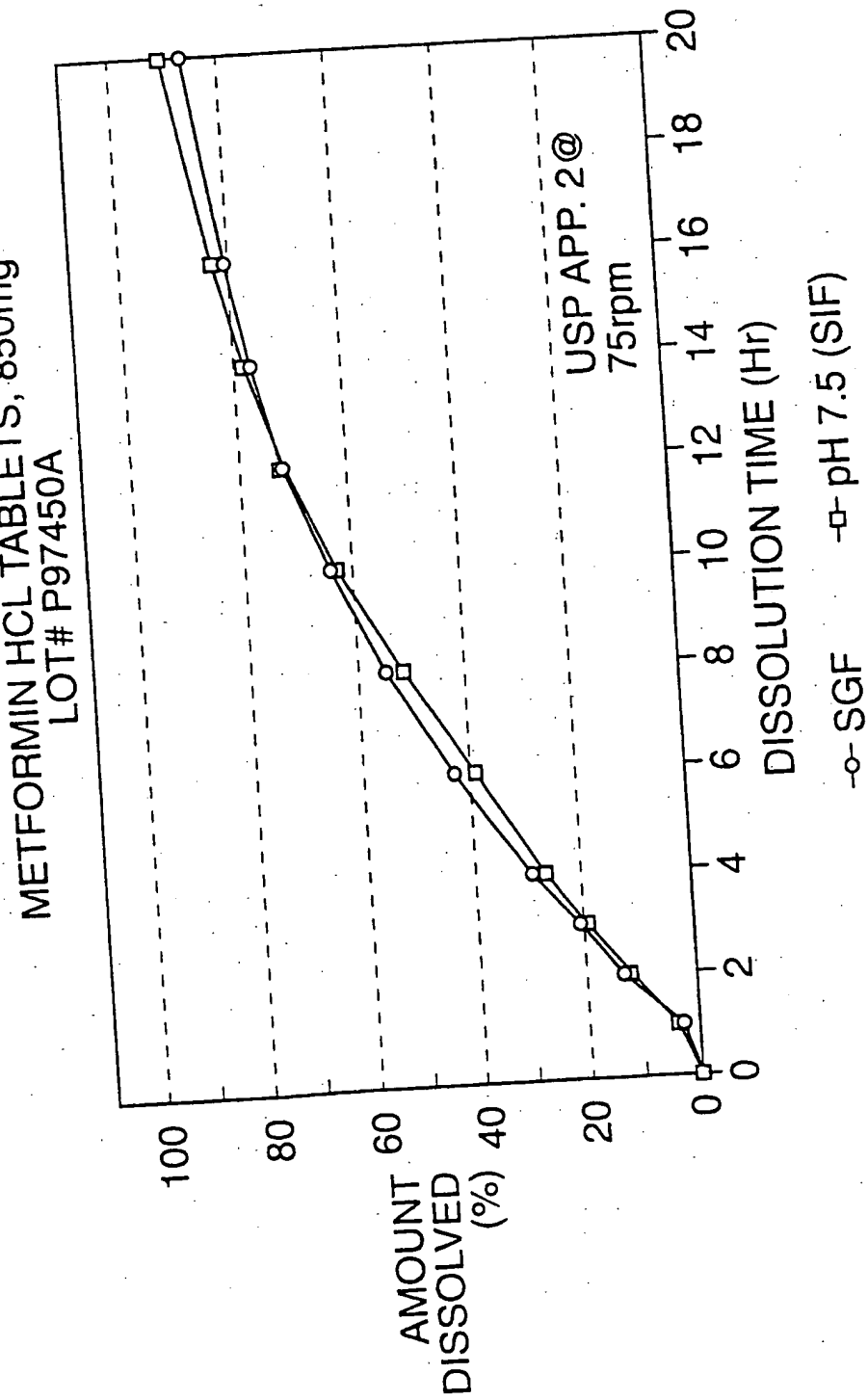


FIG. 2

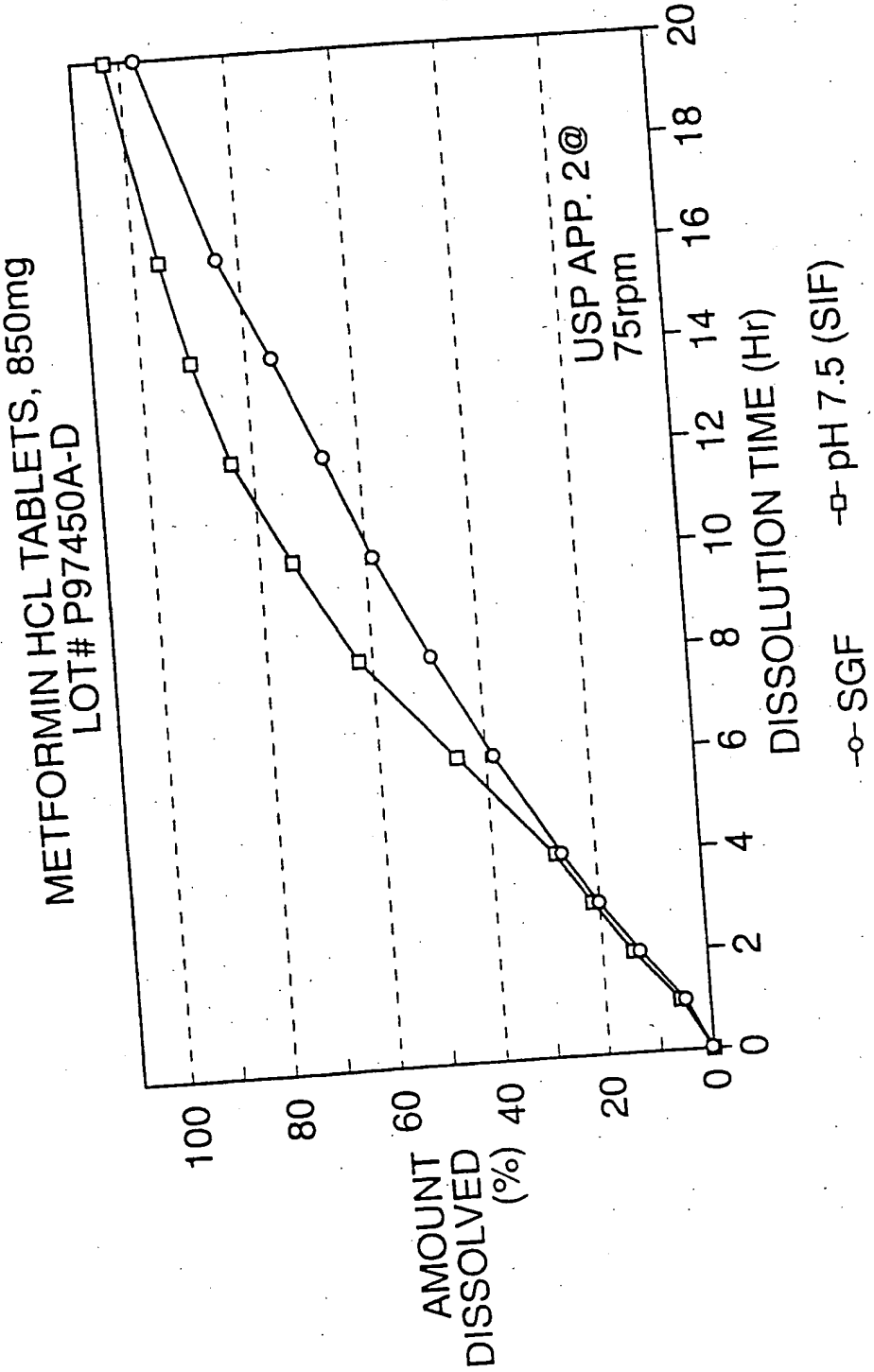


FIG. 3

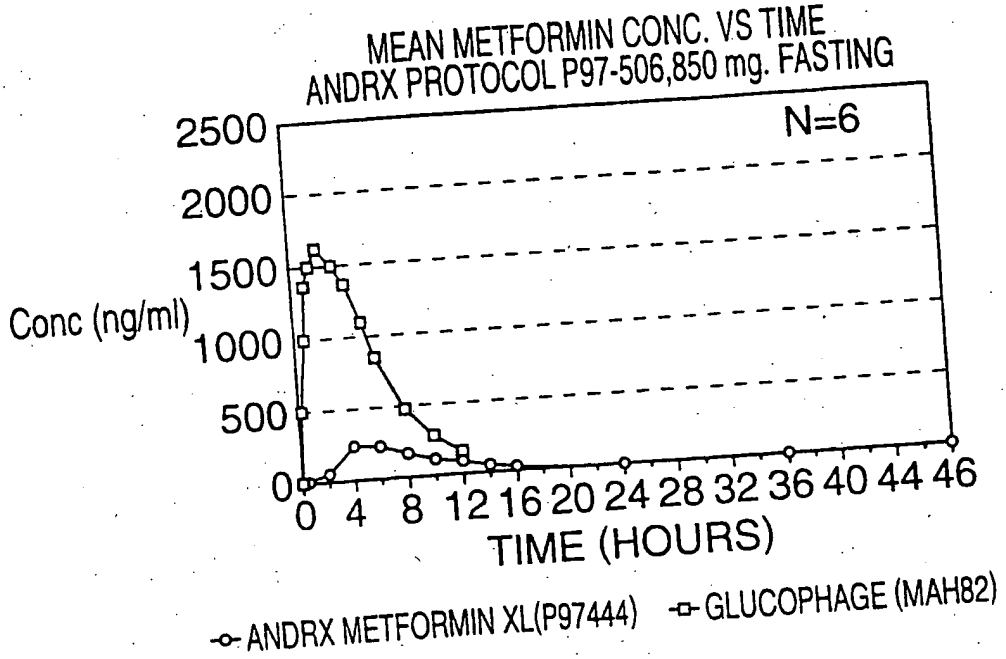


FIG. 4

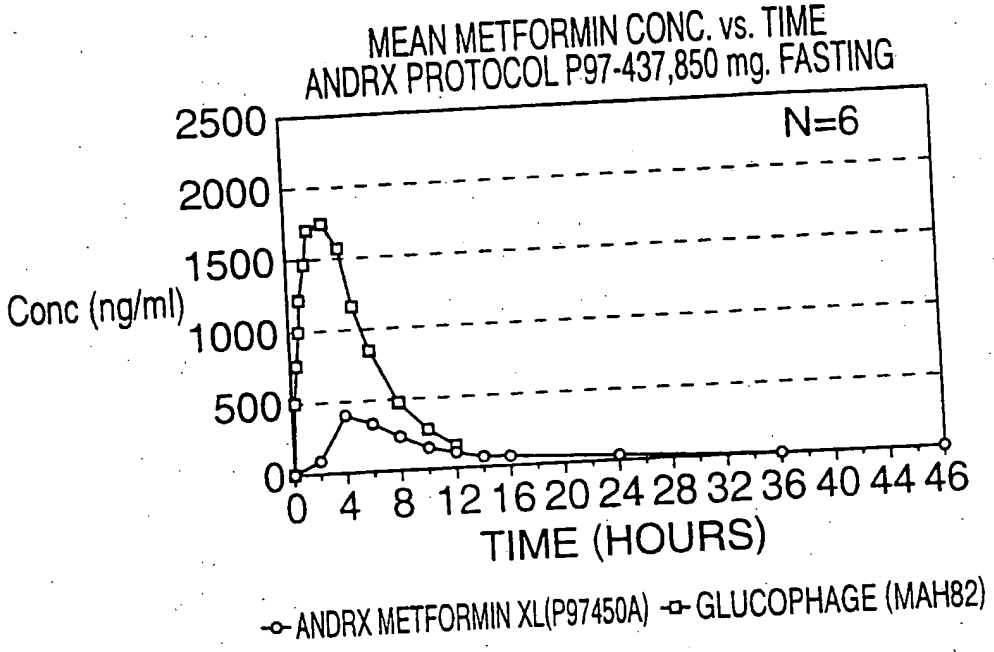


FIG. 5

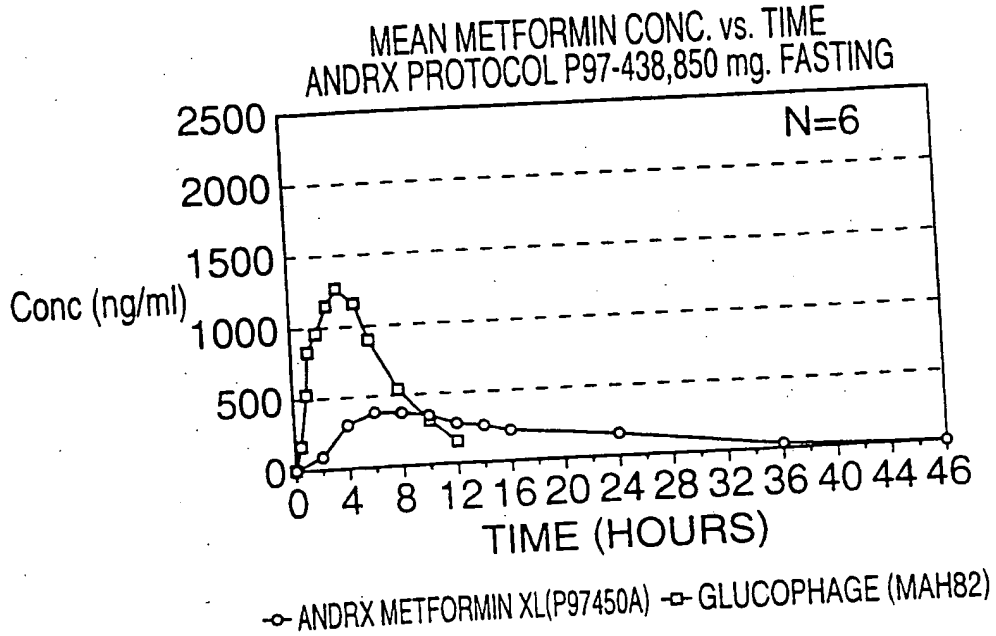


FIG. 6

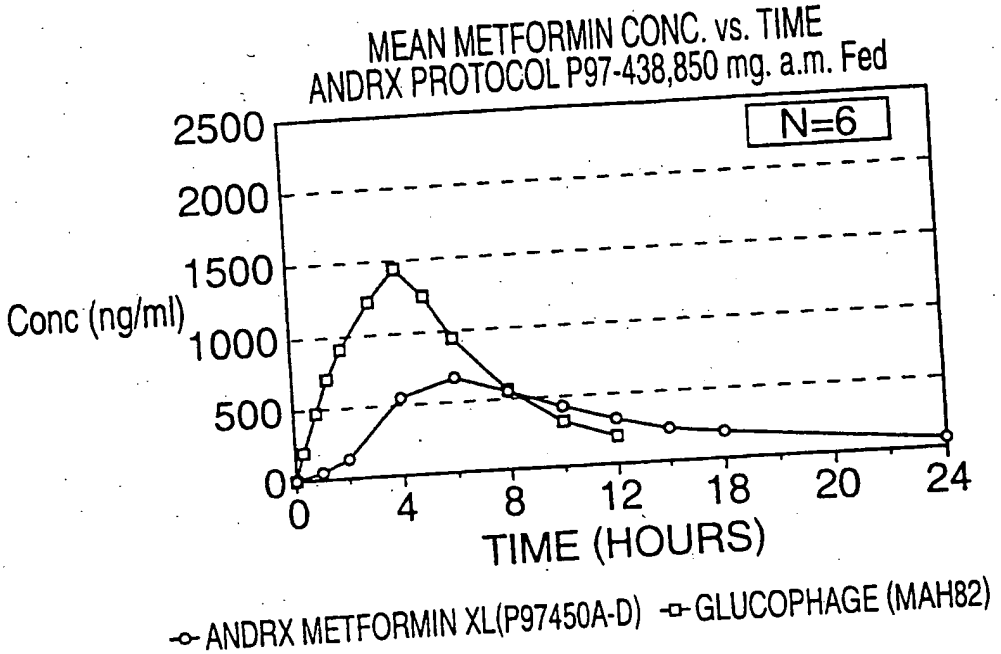


FIG. 7

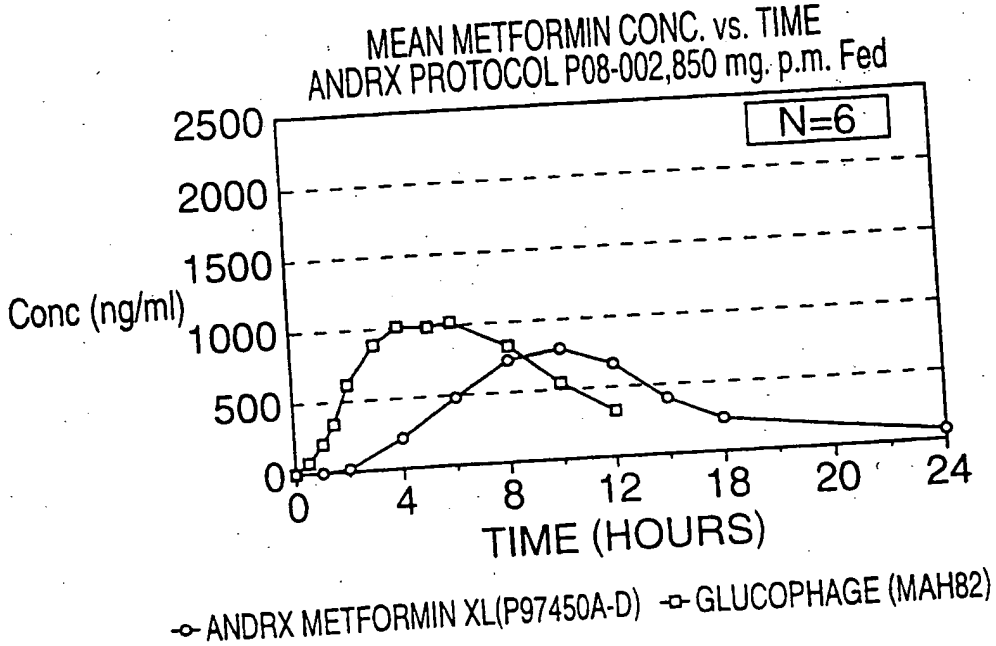


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06024

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/20
US CL :424/464

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464

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

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

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,858,398 A (CHO) 12 JANUARY 1999, col. 1, lines 13-16; col. 3, lines 18-28; col. 11, lines 25-35; col. 12, lines 13-29, col. 15, lines 10,63; col. 16, lines 1-19; col. 18, lines 32-35; col. 19, lines 67; col. 20 lines 1-5.	1-30

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

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

Date of the actual completion of the international search 21 APRIL 1999	Date of mailing of the international search report 24 JUN 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. Lawrence for THURMAN K. PAGE Telephone No. (703) 308-1235

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

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/155

A1

(11) International Publication Number: WO 99/29314

(43) International Publication Date: 17 June 1999 (17.06.99)

(21) International Application Number: PCT/US98/25104

(22) International Filing Date: 1 December 1998 (01.12.98)

(30) Priority Data:
08/986,586 8 December 1997 (08.12.97) US

(71) Applicant: BRISTOL–MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543–4000 (US).

(72) Inventors: TIMMINS, Peter; 5 Heathbank Avenue, Irby, Merseyside L61 4XD (GB). WINTER, William, J.; 2166 W. Lake Road, Skaneateles, NY 13152 (US). SRIVASTAVA, Sushil, K.; 9 Kayann Drive, Dayton, NJ 08810 (US). BRETNALL, Alison; 33 Sandon Road, Newton, Chester CH2 2EP (GB). WEI, Chenkou; 44 Windsor Drive, Princeton Junction, NJ 08550 (US). POWERS, Gerald, L.; 721 Cranbury Cross Road, North Brunswick, NJ 08902 (US).

(74) Agents: RODNEY, Burton et al.; Bristol–Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543–4000 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL SALTS OF METFORMIN AND METHOD

(57) Abstract

Novel salts of the antidiabetic agent metformin are provided which are metformin salts of dibasic acids (2:1 molar ratio), preferably metformin (2:1) fumarate and metformin (2:1) succinate, which may be employed alone or in combination with another antihyperglycemic agent such as glyburide, for treating diabetes. A method for treating diabetes employing the novel metformin salt by itself or in combination with another antidiabetic agent is also provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL SALTS OF METFORMIN AND METHOD

Field of the Invention

The present invention relates to salts of the anti-diabetic agent metformin, and more particularly to metformin salts of dibasic acids, preferably dibasic organic carboxylic acids, optionally in combination with other anti-diabetic agent and to a method employing such salts or combinations for treating diabetes.

Background of the Invention

The biguanide antihyperglycemic agent metformin is concurrently marketed in the U.S. in the form of its hydrochloride salt (Glucophage™, Bristol-Myers Squibb Company).

Metformin hydrochloride is a cohesive white powder which is highly soluble in water (>300 mg/ml at ambient temperature), has a hygroscopicity measured at 95% relative humidity /25°C of greater than 20% moisture uptake at 6 hours, and a high compaction susceptibility. Accordingly, handling of metformin hydrochloride in a pharmaceutical manufacturing facility could present problems especially in high humidity environments. Furthermore, formulation of the metformin hydrochloride in a controlled release system is exceedingly difficult due, at least in part, to its extremely high water solubility .

The currently marketed metformin hydrochloride salt has a pronounced saline, bitter taste. Accordingly, it is usually marketed as a coated tablet where the coating is designed to mask any unpleasant taste. However, where the metformin hydrochloride salt is in the form of scored-divisible tablets, it will not usually have a coating or outer layer to mask the unpleasant taste.

Taste is of primary concern where the metformin hydrochloride is to be formulated as a chewable tablet or liquid indicated for children or adults who are not able to swallow tablets.

In such cases, the unpleasant taste of the hydrochloride salt could lead to compliance problems.

The prior art is replete with references disclosing metformin salts of various organic or inorganic acids in a 1:1 molar ratio of metformin:acid. Thus, for example, U.S. Patent No. 3,174,901 discloses phosphate, sulfate, hydrobromide, salicylate, maleate, benzoate, succinate, ethanesulfonate, fumarate and glycolate salts of metformin;

U.S. Patent No. 4,835,184 discloses the p-chlorophenoxyacetic acid salt of metformin;

French Patent Nos. 2320735 and 2037002 disclose the pamoate salt of metformin;

French Patent No. 2264539 and Japanese Patent No. 66008075 disclose the orotate salt of metformin;

French Patent No. 2275199 discloses the (4-chlorophenoxy)isobutyrate salt of metformin;

U.S. Patent No. 4,080,472 discloses the clofibrate salt of metformin;

U.S. Patent No. 3,957,853 discloses the acetylsalicylate salt of metformin;

French Patent No. 2220256 discloses the theophyllin-7-acetate salt of metformin;

German Patent Nos. 2357864 and 1967138 disclose the nicotinic acid salt of metformin;

U.S. Patent No. 3,903,141 discloses the adamantoate salt of metformin;

Japanese Patent No. 69008566 discloses the zinc-chlorophyllin salt of metformin;

Japanese Patent No. 64008237 discloses hydroxy acid salts of metformin, including salts of hydroxy aliphatic dicarboxylic acids such as mesotartaric acid, tartaric acid, mesoxalic acids, and oxidized maleates;

Japanese Patent No. 63014942 discloses the tannic acid salt of metformin;

Japanese Patent Nos. 87005905 and 61022071 disclose the 3-methyl-pyrazole-5-carboxylic acid (or other 5-members hetercycle carboxylic acid) salt of metformin;

Romanian Patent No. 82052 discloses sulfamido aryloxyalkyl carboxylic acid salts of metformin;

Soviet Union Patent No. 992512 discloses the trimethoxy benzoic acid salt of metformin;

U.S. Patent No. 4,028,402 discloses the dichloroacetic acid salt of metformin.

All of the above salts are formed of metformin: salt in a 1:1 molar ratio.

U.S. Patent No. 5,631,224 to Efendic et al issued May 20, 1997, discloses a combination of metformin with GLP-1(7-36) amide, or GLP-1(7-37) or a fragment thereof which retains GLP-1(7-37) activity.

Description of the Invention

In accordance with the present invention, novel salts of metformin are provided which retain equivalent antihyperglycemic activity to metformin hydrochloride, but which have improved handling properties as compared to metformin hydrochloride salt, including lower hygroscopicity and better flow properties as well as reduced compaction susceptibility and reduced corrosiveness such as to tablet tooling. The novel salts of the invention will also have improved taste properties as compared to the hydrochloride salt thus enhancing patient compliance, especially where the novel salts are in the form of scored tablets, chewable tablets or liquids.

In addition, the novel salts of metformin of the invention are significantly less soluble in water than the hydrochloride salt and thus provide the opportunity for formulating metformin in controlled release systems which require less polymer excipients to achieve a desired metformin release rate.

The novel metformin salts of the invention are metformin salts of dibasic acids wherein the molar ratio of metformin:dibasic acid is 2:1.

The dibasic aid forming the novel salt with metformin is preferably a dibasic organic carboxylic acid

which includes saturated dicarboxylic acids such as succinic acid, malonic acid, glutaric acid, adipic acid, and pimelic acid and unsaturated dicarboxylic acids such as fumaric acid, maleic acid, and hydroxydicarboxylic acids such as malic acid, tartronic acid, and tartaric acid. Most preferred are the metformin (2:1) salt of succinic acid and the metformin (2:1) salt of fumaric acid.

The preferred metformin (2:1) fumarate salt of the invention is a free-flowing white crystalline solid which has a solubility in water at ambient temperature of 140 mg salt per ml water.

The preferred metformin (2:1) succinate salt of the invention is a free-flowing white powder which has a solubility in water at ambient temperature of 95 mg salt per ml water.

Moreover, metformin hydrochloride is a cohesive white powder which has a high solubility in water at ambient temperature of greater than 300 mg metformin per ml water.

The metformin (2:1) fumarate salt and metformin (2:1) succinate salt of the invention each has a low hygroscopicity measured at 95% relative humidity at 25°C of less than 7% moisture uptake at 6 hours; while metformin hydrochloride has a high hygroscopicity measured at 95% relative humidity of greater than 20% moisture uptake at 6 hours.

Furthermore, the metformin (2:1) salts of the invention have reduced compaction susceptibility (tendency of the salt to compact under its own weight) as compared to the high compaction susceptibility of the metformin hydrochloride salt which could cause problems in bulk transport.

Accordingly, the novel metformin (2:1) salts of the invention with their lower hygroscopicity and improved flow properties and reduced compaction susceptibility, provide substantial and unexpected benefits over metformin

hydrochloride in terms of handling during tabletting manufacture.

Surprisingly, it has also been found that the metformin (2:1) fumarate salt and the metformin (2:1) succinate salt have a substantially more tolerable taste as compared to the metformin hydrochloride salt. Accordingly, fumarate and succinate salts of the invention may be formulated as scored tablets, as well as chewable tablets or liquids without having an adverse effect on patient compliance.

The metformin (2:1) salts of dibasic acids of the invention are prepared employing conventional salt forming procedures. Thus, for example, the metformin base (which may be prepared from the hydrochloride using an ion-exchange column or other conventional technique) is dissolved in methanol or other suitable solvent and then admixed with a solution of the dibasic organic carboxylic acid, such as fumaric acid or succinic acid, in ethanol or other suitable solvent (in a 2:1 molar ratio metformin:dibasic acid). The desired salt crystallizes out and may be recovered by filtration, and dried to form a free flowing solid.

Still further in accordance with the invention, novel antihyperglycemic combinations are provided which include a metformin salt of a dibasic acid (2:1 molar ratio) in combination with another antihyperglycemic agent which may be administered orally or by injection.

The use of the metformin salt of the invention in combination with another anti-hyperglycemic agent produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antihyperglycemic agent may be an oral antihyperglycemic agent preferably a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide,

gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide being preferred.

The metformin salt of the invention will be employed in a weight ratio to the sulfonyl urea in the range from about 300:1 to about 50:1, preferably from about 250:1 to about 75:1.

The oral antihyperglycemic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436).

The metformin salt of the invention will be employed in a weight ratio to the glucosidase inhibitor within the range from about 300:1 to about 2:1, preferably from about 200:1 to about 25:1.

The metformin salt of the invention may be employed in combination with a thiazolidinedione oral anti-diabetic agent (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), zorglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016) Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer).

The metformin salt of the invention will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 75:1 to about 0.1:1, preferably from about 5:1 to about 0.5:1.

The novel metformin salt of the invention may also be employed in combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be

administered via injection, orally, or by transdermal or buccal devices.

The novel metformin salts of the invention alone or in combination with another antihyper-glycemic agent may also be employed in combination with amylin.

In addition, in accordance with the present invention a method is provided for treating hyperglycemia including Type II diabetes (NIDDM) and/or Type I diabetes (IDDM) wherein a therapeutically effective amount of a metformin salt of a dibasic acid (2:1 molar ratio), optionally in combination with another antihyperglycemic agent, is administered to a patient in need of treatment.

Where present, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol may be employed in formulations, amounts and dosing as indicated in the Physician's Desk Reference.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The novel metformin salts of the present invention are potent anti-hyperglycemic agents at least equivalent to metformin hydrochloride and can be administered to various mammalian species, such as dogs, cats, humans, etc., in need of such treatment in the same manner as metforin hydrochloride. These metformin salts can be administered systemically, preferably orally.

The metformin salts of the invention alone or in combination with one or more oral antihyperglycemic agents can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms of the metformin (2:1) salt of the invention (whether by itself or with another antihyperglycemic agent) described above may be administered in amounts as described for metformin hydrochloride (Bristol-Myers Squibb Company's Glucophage®) as set out in the Physician's Desk Reference.

The combination of the metformin salt of the invention and the other antihyperglycemic agent may be formulated separately or, where possible, in a single formulation employing conventional formulation procedures.

The various formulations of the invention may optionally include one or more fillers or excipients in an amount within the range of from about 0 to about 90% by weight and preferably from about 1 to about 80% by weight such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium carbonate and/or cellulose derivatives such as wood cellulose and microcrystalline cellulose.

One or more binders may be present in addition to or in lieu of the fillers in an amount within the range of from about 0 to about 35% and preferably from about 0.5 to about 30% by weight of the composition. Examples of such binders which are suitable for use herein include polyvinylpyrrolidone (molecular weight ranging from about

5000 to about 80,000 and preferably about 40,000), lactose, starches such as corn starch, modified corn starch, sugars, gum acacia and the like as well as a wax binder in finely powdered form (less than 500 microns) such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

Where the composition is to be in the form of a tablet, it will include one or more tablet disintegrants in an amount within the range of from about 0.5 to about 10% and preferably from about 2 to about 8% by weight of the composition such as croscarmellose sodium, povidone, crospovidone, sodium starch glycolate, corn starch or microcrystalline cellulose as well as one or more tableting lubricants in an amount within the range of from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition, such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax and the like. Other conventional ingredients which may optionally be present include preservatives, stabilizers, anti-adherents or silica flow conditioners or glidants, such as Syloid brand silicon dioxide as well as FD&C colors.

Tablets of the invention may also include a coating layer which may comprise from 0 to about 15% by weight of the tablet composition. The coating layer which is applied over the tablet core may comprise any conventional coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxy-propylmethyl cellulose and a hydrophobic polymer like ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, β-pinene polymers, glyceryl esters of wood resins and the like and one or more plasticizers, such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil and the like. Both core tablets as well as coating formulations may contain aluminum lakes to provide color.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols like methyl alcohol, ethyl alcohol or isopropyl alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

Where a color is employed, the color will be applied together with the film former, plasticizer and solvent compositions.

A preferred tablet composition of the invention will include from about 90 to about 97.5% by weight metformin (2:1) salt from about 2 to about 8% by weight providone, and from about 0.5 to about 2% by weight magnesium stearate.

The pharmaceutical composition of the invention may be prepared as follows. A mixture of the medicament and a fraction (less than 50%) of the filler where present (such as lactose), with or without color, are mixed together and passed through a #12 to #40 mesh screen. Filler-binder where present (such as microcrystalline cellulose), disintegrant (such as providone) are added and mixed. Lubricant (such as magnesium stearate) is added with mixing until a homogeneous mixture is obtained.

The resulting mixture may then be compressed into tablets of up to 2 grams in size.

Where desired, the tablets of the invention may be formulated by a wet granulation techniques as disclosed in U.S. Patent No. 5,030,447 which is incorporated herein by reference.

The following examples represent preferred embodiments of the invention.

Example 1

Preparation of Metformin (2:1) Fumarate

Metformin base (8.71 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H_2O [5:1]. With stirring, a solution of fumaric acid (4.05 moles) in ethanol was added over a period of one hour under a nitrogen atmosphere at ambient temperature (~20°C). Crystallization began to occur immediately. After stirring the slurry for one hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to afford the metformin (2:1) fumarate salt as a free-flowing white crystalline solid in 72 M% yield and melting point of 247-249°C.

The resulting metformin (2:1) fumarate salt had a solubility in water (mg/ml) of 140, a hygroscopicity measured at 95% relative humidity/25°C of less than 7% moisture uptake at 6 hours, and a low compaction susceptibility. Tabletting of the metformin (2:1) fumarate salt resulted in reduced corrosion of tablet tooling equipment as compared with the corresponding hydrochloride salt.

Example 2

Preparation of Metformin (2:1) Succinate

Metformin base (8.95 moles) (prepared from the hydrochloride salt via an ion-exchange column) was dissolved in methanol/H_2O [5:1]. With stirring, a solution of succinic acid (4.42 moles) in ethanol was added over one hour under a nitrogen atmosphere at ambient temperature (~20°C). Crystallization of the salt commenced shortly after addition of the succinic acid solution. After stirring the slurry for an hour at ambient temperature, the product was filtered off, washed with ethanol and dried under vacuum to form the metformin (2:1) succinate salt as

a free flowing white crystalline solid in 89 M% yield and melting point of 246-247°C.

The resulting metformin (2:1) succinate salt had a solubility in water (mg/ml) of 95, a hygroscopicity measured at 95% relative humidity/25°C of less than 1% moisture uptake at 30 minutes, and a low compaction susceptibility. Tabletting of the metformin (2:1) fumarate salt resulted in reduced corrosion of tablet tooling equipment as compared with the corresponding hydrochloride salt.

Example 3
Preparation of Tablets Containing Metformin (2:1) Fumarate

Tablets of the following formulation were prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) fumarate	600.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Povidone USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer metformin (2:1) fumarate was blended with half the microcrystalline cellulose and with the croscarmellose sodium. The povidone USP was dissolved in a suitable quantity of purified water and this solution was used to wet granulate the drug-excipient mixture. The granules were dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules were mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix was compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is the case with metformin hydrochloride formulations in order to ensure trouble free tabletting.

The metformin fumarate salt has a less intense taste than metformin hydrochloride which means film coating of the final metformin fumarate tablet is not necessary.

Example 4

Preparation of Tablets Containing Metformin (2:1) Succinate

Tablets of the following formulation are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Hydroxypropylmethyl cellulose (5 cps) (HPMC) USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer the metformin (2:1) succinate is blended with half the microcrystalline cellulose and with the croscarmellose sodium. The HPMC USP is dispersed in a suitable quantity of purified water and this mixture is used to wet granulate the drug-excipient mixture. The granules are dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules are mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix is compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is

the case with metformin hydrochloride formulations in order to ensure trouble free tabletting.

Example 5

Preparation of Tablets Containing Metformin (2:1) Fumarate and Glyburide

Tablets of the following formulation are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) fumarate	600.0 mg
Glyburide	5.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Povidone USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer metformin (2:1) fumarate is blended with half the microcrystalline cellulose and with the croscarmellose sodium. The povidone USP is dissolved in a suitable quantity of purified water and this solution is used to wet granulate the drug-excipient mixture. The granules are dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules are mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix is compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is the case with metformin hydrochloride formulations in order to ensure trouble free tabletting, and the less intense taste of the fumarate salt means film coating of the final tablet may not be necessary.

Example 6

Preparation of Tablets Containing Metformin (2:1) Succinate and Glyburide

Tablets of the following formulations are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Glyburide	5.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Hydroxypropylmethyl cellulose (5 cps) USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer metformin (2:1) succinate and glyburide are blended with half the microcrystalline cellulose and with the croscarmellose sodium. The HPMC USP is dissolved in a suitable quantity of purified water and this solution is used to wet granulate the drug-excipient mixture. The granules are dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules are mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix is compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is the case with metformin hydrochloride formulations in order to ensure trouble free tabletting.

Example 7
Preparation of Tablets Containing Metformin (2:1) Fumarate and Glipizide

Tablets of the following formulations are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) fumarate	600.0 mg
Glipizide	5.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Povidone USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer metformin (2:1) fumarate and glipizide are blended with half the microcrystalline cellulose and with the croscarmellose sodium. The povidone USP is dissolved in a suitable quantity of purified water and this solution is used to wet granulate the drug-excipient mixture. The granules are dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules are mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix is compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is the case with metformin hydrochloride formulations in order to ensure trouble free tabletting.

Example 8
Preparation of Tablets Containing Metformin (2:1) Succinate and Glipizide

Tablets of the following formulations were prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Glipizide	5.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Hydroxypropyl methyl cellulose (5 cps) USP	15.0 mg
Magnesium Stearate NF	8.0 mg

In a planetary mixer metformin (2:1) succinate and glipizide are blended with half the microcrystalline cellulose and with the croscarmellose sodium. The HPMC USP is dissolved in a suitable quantity of purified water and this mixture is used to wet granulate the drug-excipient mixture. The granules are dried in an oven at 60°C to a moisture content of 1.5-2.5% w/w. In a V-cone blender the granules are mixed with the remaining microcrystalline cellulose and then with the magnesium stearate. The resulting mix is compressed into tablets using suitable capsule shaped tooling.

This formulation does not require introduction of additional moisture immediately prior to compression as is the case with metformin hydrochloride formulations in order to ensure trouble free tabletting.

Example 9

Preparation of Chewable Tablets Containing Metformin (2:1) Fumarate Salt

Chewable tablets of the following formulation are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Xylitol	450.0 mg
Flavor, grape	0.5 mg
Flavor, spice	0.5 mg
Magnesium Stearate NF	10.0 mg

The metformin (2:1) fumarate is passed through a suitable wire mesh screen (600 micron aperture). The flavor ingredients are blended with the pre-screened xylitol and the resulting mix is added to the metformin (2:1) fumarate in a V-cone blender. The mixture is mixed for ten minutes. The magnesium stearate is added to the contents of the V-cone blender, passing the magnesium stearate through a 425 micron aperture screen. The mix is mixed for 5 minutes and compressed into flat faced bevel edged tablets using suitable tooling.

Example 10

Preparation of Chewable Formulation of Metformin (2:1) Succinate Salt

Chewable tablets of the following formulation are prepared as described below.

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Xylitol	450.0 mg
Flavor, raspberry	0.5 mg
Magnesium Stearate NF	10.0 mg

The metformin (2:1) succinate is passed through a suitable wire mesh screen (600 micron aperture). The flavor ingredient is blended with the pre-screened xylitol and the resulting mix is added to the metformin (2:1) succinate in a V-cone blender. The mixture is mixed for ten minutes. The magnesium stearate is added to the contents of the V-cone blender, passing the magnesium stearate through a 425 micron aperture screen. The mix is mixed for 5 minutes and compressed into flat faced bevel edged tablets using suitable tooling.

Example 11

The following experiment was carried out to determine moisture sorption/desorption profiles of metformin (2:1) fumarate salt and metformin (2:1) succinate salt compared to the moisture uptake properties of metformin hydrochloride salt.

The procedure employed was as follows:

The hygroscopicity of metformin salts was assessed by Dynamic Vapour Sorption (DVS), a means of rapidly assessing sample moisture uptake properties. Approximately 5 mg of sample is placed on a suitable microbalance sample pan in a controlled temperature environment (held at 30°C) and which is suitably tared against a separate blank pan. Both chambers are subjected to a controlled program of incremental increase in RH from 0% to 95% by means of a moisture saturated air/dry nitrogen variable mixture gas stream. The weight increase of sample at each condition is recorded until a defined minimal rate of mass change is reached or a specified time period for equilibrium exceeded. A reverse cycle from 95% to 0% is performed immediately, allowing an absorption and desorption profile to be generated and from which the hygroscopicity was determined.

The following moisture uptake at 95% relative humidity/25°C is observed.

(1) metformin hydrochloride	Time	% moisture uptake
	30 min	1.2%
	70 min	3.3%
	3 hours	10.0%
	6 hours	20.1%
	(did not reach equilibrium)	

(2) metformin (2:1) fumarate	Time	% moisture uptake
	30 min	1.0%
	70 min	2.0%
	3 hours	4.1%
	6 hours	6.6%
	(did not reach equilibrium)	

(3) metformin (2:1) succinate	Time	% moisture uptake
	30 min	0.27%
	(reached equilibrium)	

In summary, the degree of moisture uptake for the salts tested were found to occur in the following rank order:

(1) metformin hydrochloride salt: 20% moisture content after 6 hours at 95% relative humidity at 25°C

(2) metformin (2:1) fumarate salt: 6.6% moisture after 6 hours at 95% relative humidity at 25°C

(3) metformin (2:1) succinate:	0.27% equilibrium moisture content after 30 minutes at 95% relative humidity at 25°C.

From the above results, it is seen that metformin hydrochloride salt absorbs substantially greater amounts of moisture as compared to the metformin (2:1) fumarate salt of the invention and the metformin (2:1) succinate salt of the invention. Accordingly, the metformin (2:1) salts of the invention will have improved handling properties during tabletting as compared to the metformin hydrochloride salt.

What is claimed is:

1. A metformin salt of a dibasic acid in a molar ratio of 2 moles metformin to 1 mole dibasic acid.

2. The metformin salt as defined in Claim 1 wherein the dibasic acid is a dibasic organic carboxylic acid.

3. The metformin salt as defined in Claim 1 which is metformin (2:1) fumarate.

4. The metformin salt as defined in Claim 1 which is metformin (2:1) succinate.

5. The metformin salt as defined in Claim 1 which is metformin (2:1) malate.

6. The metformin salt as defined in Claim 1 which is in the form of free flowing powder or crystals.

7. A metformin salt of a dibasic acid having a solubility in water (mg/ml) at ambient temperature of less than about 150 mg/ml.

8. A metformin salt of a dibasic acid in the form of free flowing granules having a hygroscopicity measured at 95% relative humidity, 20°C of less than 7% moisture uptake at 6 hours.

9. A pharmaceutical composition comprising a metformin salt as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

10. The pharmaceutical composition as defined in Claim 9 in the form of a tablet or capsule and the metformin salt is metformin fumarate or metformin succinate.

11. The pharmaceutical composition as defined in Claim 9 further including another antihyperglycemic agent.

12. The pharmaceutical composition as defined in Claim 11 wherein the other antihyperglycemic agent is glyburide or glipizide.

13. A method for treating hyperglycemia which comprises administering to a patient in need of treatment a therapeutically effective amount of a metformin salt as defined in Claim 1.

14. The method as defined in Claim 13 wherein the metformin salt is administered with a therapeutically effective amount of another antihyperglycemic agent.

15. The method as defined in Claim 14 wherein the other antihyperglycemic agent is glyburide or glipizide.

16. A combination of a metformin salt of a dibasic acid in a molar ratio of 2 moles metformin to 1 mole dibasic acid, and another antihyperglycemic agent.

17. The combination as defined in Claim 16 wherein the metformin salt is metformin (2:1) fumarate or metformin (2:1) succinate.

18. The combination as defined in Claim 16 wherein the other antihyperglycemic agent is a sulfonyl urea, a glucosidase inhibitor, a thiazolidinedione, a GLP-1 peptide, and/or insulin.

19. The combination ad defined in Claim 18 wherein the antihyperglycemic agent is glyburide, glipizide, glimepiride, acarbose, miglitol, troglitazone or insulin.

20. The combination as defined in Claim 16 which is metformin (2:1) fumarate or metformin (2:1) succinate, and glyburide or glipizide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25104

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/155
US CL : 514/635
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/635

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,174,901 A (STERNE et al) 23 March 1965, see the entire document.	1-20

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
19 JANUARY 1999	03 FEB 1999

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

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

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT

WELTORGANISATION FÜR GEIST
Internationales Bür

INTERNATIONALE ANMELDUNG VERÖFFENTLIC
INTERNATIONALE ZUSAMMENARBEIT AUF DEM

WO 9608243A1

AN

(51) Internationale Patentklassifikation 6 :
A61K 31/155, 9/20

A1

(11) Internationale Veröffentlichungsnummer: WO 96/08243

(43) Internationales Veröffentlichungsdatum: 21. März 1996 (21.03.96)

(21) Internationales Aktenzeichen: PCT/EP95/03610

(22) Internationales Anmeldedatum: 14. September 1995 (14.09.95)

(30) Prioritätsdaten:
P 44 32 757.9 14. September 1994 (14.09.94) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: BOEHRINGER MANNHEIM GMBH [DE/DE]; D-68298 Mannheim (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: MOECKEL, Jörn [DE/DE]; Am Baechenbuckel 24/1, D-69118 Heidelberg (DE). GABEL, Rolf-Dieter [DE/DE]; Kurpfalzring 96, D-68723 Schwetzingen (DE). WOOG, Heinrich [DE/DE]; Lindenstrasse 6, D-69514 Laudenbach (DE).

(74) Anwälte: MINK, Reinhold usw.; Boehringer Mannheim GmbH, Patentabteilung, D-68298 Mannheim (DE).

(81) Bestimmungsstaaten: AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SI, SK, UA, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND A PROCESS FOR PRODUCING IT

(54) Bezeichnung: PHARMAZEUTISCHE ZUBEREITUNG ENTHALTEND METFORMIN UND VERFAHREN ZU DEREN HERSTELLUNG

(57) Abstract

The present invention concerns pharmaceutical compounds containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and (optionally) standard pharmaceutical auxiliary substances, the residual moisture content in the proposed pharmaceutical compound being 0.5-3 % by weight. The invention also concerns a process for producing pharmaceutical compounds containing metformin as an active substance and a hydrocolloid-forming agent as a retardant, and (optionally) standard pharmaceutical auxiliary substances. The proposed process is characterized by the fact that the active substance and retarding agent, or a portion thereof, are granulated with an aqueous solvent which can optionally contain a binder, and where appropriate the other portion of the retardant or other standard pharmaceutical auxiliaries are mixed with the granulate which is then dried until the residual moisture content is reduced to 0.5-3 % by weight.

(57) Zusammenfassung

Gegenstand der vorliegenden Erfindung sind pharmazeutische Zusammensetzungen enthaltend Metformin als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel sowie gegebenenfalls pharmazeutisch übliche Hilfsstoffe, wobei die Restfeuchte in der pharmazeutischen Zusammensetzung 0,5-3 Gew.-% beträgt. Die Erfindung betrifft ferner ein Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen enthaltend Metformin als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel sowie gegebenenfalls weitere pharmazeutisch übliche Hilfsstoffe, dadurch gekennzeichnet, daß man den Wirkstoff und das Retardierungsmittel oder ein Teil davon mit einem wäßrigen, gegebenenfalls bindemittelhaltigen Lösungsmittel granuliert, gegebenenfalls den anderen Teil des Retardierungsmittels oder andere pharmazeutisch übliche Hilfsmittel dem Granulat zumischt, und anschließend das Granulat bis zu einer Restfeuchte von 0,5-3 Gew.-% trocknet.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AT	Österreich
AU	Australien
BB	Barbados
BE	Belgien
BF	Burkina Faso
BG	Bulgarien
BJ	Benin
BR	Brasilien
BY	Belarus
CA	Kanada
CF	Zentrale Afrikanische Republik
CG	Kongo
CH	Schweiz
CI	Côte d'Ivoire
CM	Kamerun
CN	China
CS	Tschechoslowakei
CZ	Tschechische Republik
DE	Deutschland
DK	Dänemark
ES	Spanien
FI	Finnland
FR	Frankreich
GA	Gabon
GB	Vereinigtes Königreich
GE	Georgien
GN	Guinea
GR	Griechenland
HU	Ungarn
IE	Irland
IT	Italien
JP	Japan
KE	Kenya
KG	Kirgisistan
KP	Demokratische Volksrepublik Korea
KR	Republik Korea
KZ	Kasachstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxemburg
LV	Lettland
MC	Monaco
MD	Republik Moldau
MG	Madagaskar
ML	Mali
MN	Mongolei
MR	Mauretanien
MW	Malawi
NE	Niger
NL	Niederlande
NO	Norwegen
NZ	Neuseeland
PL	Polen
PT	Portugal
RO	Rumänien
RU	Russische Föderation
SD	Sudan
SE	Schweden
SI	Slowenien
SK	Slowakei
SN	Senegal
TD	Tschad
TG	Togo
TJ	Tadschikistan
TT	Trinidad und Tobago
UA	Ukraine
US	Vereinigte Staaten von Amerika
UZ	Usbekistan
VN	Vietnam

Pharmazeutische Zubereitung enthaltend Metformin und Verfahren zu deren Herstellung

Die Erfindung betrifft pharmazeutische Zubereitungen enthaltend Metformin-Hydrochlorid (im folgenden auch Metformin genannt) als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel und ein Verfahren zu deren Herstellung.

Es ist bekannt, daß Metformin-Hydrochlorid ein Biguanidderivat ist (1,1-Dimethylbiguanid-Monohydrochlorid), das oral antidiabetisch wirkt. Metformin-Retardtabletten sind mit 850 mg Metformin-Hydrochlorid pro Filmtablette (Glucophage® retard) auf dem Markt. Da sich Metformin im Gegensatz zu anderen Wirkstoffen als Reinsubstanz nicht verpressen läßt (die Masse zerfällt nach dem Komprimieren unverändert), wurde bei diesen hochdosierten Retardtabletten auf gerüstbildende Hilfsstoffe wie Polyvinylacetat als Retardierungsmittel zurückgegriffen (Lipha, Fachinformation Glucophage®. August 1991; Bundesverband der Pharmazeutischen Industrie e.V., Hrsg., Rote Liste 1993, Edition Cantor, Aulendorf 1993). Die Wirkungsweise solcher Gerüsttabletten beruht darauf, daß das gut wasserlösliche Metformin im Magen-Darm-Trakt pH-unabhängig aus der Tablette herausdiffundiert, während das Tablettengerüst mit Überzug weitgehend unverändert wieder ausgeschieden wird.

Der Nachteil der Verwendung solcher gerüstbildenden Hilfsstoffe wie Polyvinylacetat beruht jedoch darauf, daß sie insbesondere beim Granulationsvorgang mit organischen Lösungsmitteln verarbeitet werden müssen, wobei das organische Lösungsmittel möglichst wieder vollständig entfernt werden muß, bevor das Granulat zu komprimierten pharmazeutischen Darreichungsformen weiterverarbeitet und beispielsweise zu Tabletten verpreßt wird.

Aufgabe der Erfindung war es, eine verbesserte pharmazeutische Zusammensetzung für den Wirkstoff Metformin zur Verfügung zu stellen. Insbesondere sollte die Darreichungsform den Wirkstoff Metformin mit einem möglichst hohen Wirkstoffanteil und einem Retardierungsmittel enthalten, wobei das Retardierungsmittel eine kontrollierte

Freisetzung des Wirkstoffes bewirkt. Insbesondere sollte die neue pharmazeutische Zusammensetzung keine mit organischen Lösungsmittel zu verarbeitende Gerüstbildner enthalten, sondern auf Basis von wäßrig verarbeitbaren Substanzen aufgebaut sein. Diese pharmazeutischen Zusammensetzungen sollten gut bzw. leicht komprimierbar sein, so daß sie sich zur Herstellung von festen pharmazeutischen Darreichungsformen, wie z.B. Tabletten, Dragees oder Komprimaten zur Abfüllung in Kapseln eignen. Bei der Herstellung von Tabletten oder anderen Komprimaten sollte das Gesamtgewicht maximal etwa 1200 - 1300 mg betragen, um die Therapiesicherheit (Patienten-Compliance) nicht zu gefährden, da größere orale Darreichungsformen vom Patienten häufig nicht in der vorgeschriebenen Regelmäßigkeit eingenommen werden.

Außerdem stellte sich die Aufgabe, bei der Verarbeitung des Granulats für diese hochdosierten Darreichungsformen, insbesondere bei der Herstellung von Tabletten, das im Fall von Metformin besonders ausgeprägte wirkstoffbedingte Problem des Deckelns zu lösen, um Ausbeuteverluste während der Produktion und Beeinträchtigungen der pharmazeutischen Qualität zu vermeiden. Als Deckeln wird das Ablösen von verpreßter Masse in Schichten vom hergestellten Preßling während des Verpressens oder kurz danach bezeichnet (Schepky G. in: Bruchhausen F. von et al.; Hrsg.; Hagers Handbuch der pharmazeutischen Praxis, Band 2, Methoden, 5. Aufl., Springer Verlag, Berlin 1991). Im Fall von Metfomin, insbesondere bei hochdosierten Wirkstoffgehalten im Granulat hat sich gezeigt, daß die Tendenz des Deckelns bei der Herstellung der Tabletten besonders hoch ist.

Die Ursachen für diese Tablettierprobleme können vielfältig und komplex sein. Deckeln kann ausgelöst werden durch ungenügende Bindemittelwirkung, zu geringe oder zu hohe Granulatfeuchtigkeit, ungeeignete Kristallformen, stark aerophile Stoffe, zu hohe Porosität, zu hohen Pulveranteil, zu starke interpartikulare Bindung zwischen den Granulatkörnern sowie durch ungeeignete Granulatformen. Als maschinenbedingte Faktoren können zu hohe Preßkraft, schlecht eingesetzte oder auch abgenutzte Werkzeuge, zu hohe Preßgeschwindigkeit und schlechte Entlüftung der Matrize (starrer Druck) zum Deckeln führen. Im Falle des Wirkstoffes Metformin hat sich jedoch gezeigt, daß die üblichen Möglichkeiten nicht ausreichen, um das Deckeln der Tablettiermasse befriedigend zu beherrschen. Bei der Herstellung der Tabletten konnte regelmäßig ein relativ hoher Anteil an fehlerhaften Tabletten festgestellt werden und die Tablettierung mußte aufgrund der hohen Ausschußraten abgebrochen werden.

Im vorliegenden Fall wird die Aufgabe der Erfindung gelöst, indem hochdosierte Metformin-haltige pharmazeutische Zusammensetzungen zur Verfügung gestellt werden, die als Retardierungsmittel einen Hydrokolloidbildner enthalten und die eine Restfeuchte in der pharmazeutischen Zusammensetzung von 0,5 - 3 Gew.-% aufweisen. Diese pharmazeutischen Zusammensetzungen können vorteilhaft unter Verwendung von wäßrigen Lösungsmitteln hergestellt werden, so daß organische Lösungsmittel nicht mehr benötigt werden. Außerdem sind diese Zusammensetzungen überraschenderweise gut komprimierbar. Sie eignen sich dadurch insbesondere zur Herstellung von festen pharmazeutischen Darreichungsformen, wie z.B. Tabletten, Dragees oder Kapseln, wobei diese mit Hilfe der üblichen Verarbeitungsmaschinen in technischem Maßstab und in guter Qualität sowie in hoher Ausbeute ohne größere Verluste infolge des unerwünschten Deckelns hergestellt werden können. Gegenstand der Erfindung ist demnach auch ein entsprechendes Verfahren zur Herstellung dieser festen Darreichungsformen, indem man die entsprechenden erfindungsgemäßen pharmazeutischen Zusammensetzungen in Form von Granulaten mit einer Restfeuchte von 0,5 - 3 Gew.-% einsetzt. Vorzugsweise beträgt die Restfeuche 1 - 2,5 Gew.-%, insbesondere 1,5 - 2 Gew.-%.

Überraschenderweise wurde ferner gefunden, daß im Falle des erfindungsgemäßen Granulats auf den sonst oft erforderlichen Zusatz von Feuchthaltemittel zur Einstellung einer konstanten Restfeuchte bis zum Komprimieren des Granulates verzichtet werden kann. Dies ist insbesondere deshalb vorteilhaft, da sich der Zusatz von Hilfsstoffen somit minimieren läßt und pharmazeutische Zusammensetzungen mit einem relativ hohen Wirkstoffgehalt erhalten werden. Außerdem haben diese Zusammensetzungen den Vorteil, daß sie für einen Zeitraum von zwei Tagen oder mehr (gerechnet von der Herstellung bis zur Verwendung des Granulates zur Tablettierung) bezüglich des Feuchtegehaltes lagerstabil sind, bevor sie komprimiert werden, ohne daß eine nachteilige Veränderung der Zusammensetzung feststellbar ist. Dies ist deshalb von Vorteil, da somit mehrere Teilansätze von Produktionschargen der pharmazeutischen Zusammensetzung hergestellt werden können, und diese dann zu einem späteren Zeitpunkt in einem gemeinsamen letzten Verfahrensschritt als preßfertige Masse abgemischt und zu festen pharmazeutischen Darreichungsformen verarbeitet werden können.

Weiterhin zeigte sich überraschenderweise, daß durch die Verwendung eines Hydrokolloidbildners insbesondere die für Metformin bekannte schlechte Komprimierbarkeit erstmals technisch in zufriedenstellender Weise beherrschbar war. Die erfindungsgemäße Lösung ermöglicht zudem, daß durch die Wahl des Hydrokolloidbildners als

Retardierungsmittel und bei geeigneter Führung des Herstellprozesses (Einhalten der kritischen Restfeuchte von 0,5 - 3 % Gew.-%, insbesondere von 1 - 2,5 Gew.-% bzw. 1,5 - 2 Gew.-%) die gewünschte Retardierung und Komprimierbarkeit gewährleistet sind, obwohl der Anteil des Hydrokolloidbildners an der Rezepturzusammensetzung außergewöhnlich niedrig ist. Dies ist um so überraschender, als der überwiegende Anteil der Rezeptur (etwa 70 - 95 Gew.-%) durch den Wirkstoff gebildet wird, dessen Wassersorptionsvermögen sehr gering ist (bei einer relativen Feuchte von 90 % bindet der reine Wirkstoff lediglich 0,04 Gew.-% Wasser).

Der Gewichtsanteil des Wirkstoffes in der hochdosierten pharmazeutischen Zusammensetzung liegt im Bereich von mindestens 70 Gew.-%, vorzugsweise 80 - 95 Gew.-%, bezogen auf die pharmazeutische Zusammensetzung. Der Wirkstoff kann in Form von Säureadditionssalzen von anorganischen oder organischen Säuren, wie z.B. Salzsäure, Ameisensäure, Essigsäure, Äpfelsäure, Weinsäure oder Fumarsäure eingesetzt werden. Bevorzugt wird das Hydrochlorid-Salz eingesetzt.

Der Anteil der Hydrokolloidbildner an der pharmazeutischen Zusammensetzung beträgt bis zu 15 Gew.-%, vorzugsweise 4 - 10 Gew.-%, insbesondere etwa 6 - 8 Gew.-%.

Als Hydrokolloidbildner bzw. als hydrophile Quellstoffe im Sinne der Erfindung sind die üblichen hydrophilen Gelbildner geeignet, wie beispielsweise Cellulosederivate, Dextrine, Stärke, Polymere auf Kohlenhydratbasis, natürliche und hydrophile Gummen, Xanthane, Alginate, Gelatine, Polyacrylsäure, Polyvinylalkohol oder Polyvinylpyrrolidon. Im Falle der Cellulosederivate kommen bevorzugt die Alkyl- oder Hydroxyalkylcellulose-Derivate in Frage, wie z.B. Methylcellulose, Hydroxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Methylhydroxyethylcellulose, Methylhydroxypropylcellulose oder Natriumcarboxymethylcellulose. In einer bevorzugten Ausführungsvariante der Erfindung kommt Methylhydroxypropylcellulose (MHPC) zum Einsatz. Die Hydrokolloidbildner können sowohl einzeln als auch in Gemischen von zwei oder mehreren Kolloidbildnern verwendet werden. Als geeignete polymere Kolloidbildner auf Cellulosebasis können die üblichen für pharmazeutische Zwecke geeigneten Polymere mit unterschiedlichem Substitutionsgrad und/oder unterschiedlichem Molekulargewicht, entsprechend einem unterschiedlichen Viskositätsgrad der wäßrigen Lösung, eingesetzt werden.

Die Verwendung von Hydrokolloidbildnern als Retardierungsmittel beruht auf der Eigenschaft der Hydrokolloidbildner, daß dieser bei Kontakt mit Freisetzungsmedium oder

Verdauungssäften unter Quellung eine Gelmatrix ausbildet, die unter Erosion den Wirksoff freisetzt. Das Zusammenwirken von Hydrokolloidbildner-Menge und Viskositätsgrad bestimmt dabei den Freisetzungsverlauf. So kann beispielsweise mit einem hohen Anteil (70 - 95 %, beogen auf das Korngeweicht einer Tablette) von Polyvinylalkohol niedriger oder mittlerer Viskositätsstufe Riboflavin über mehrere Stunden retardiert werden (Möckel J E., Lippold B. C., Pharm. Research, 1993, 10, 1066 - 1070).

Die unter Verwendung der erfindungsgemäßen pharmazeutischen Zusammensetzung hergestellten komprimierten Darreichungsformen, wie beispielsweise Metformin-Retardtablettenkerne können zusätzlich mit einer Filmhülle versehen werden. Die Filmhülle kann einerseits eine zusätzliche Retardierung bewirken, indem solche Filmmaterialien eingesetzt werden, die einen für diese Zwecke üblicherweise geeigneten Filmbildner darstellen. Andererseits kann die verwendete Filmhülle ein geschmacksneutralisierender Filmbildner sein, dem gegebenenfalls Farbstoffe zugesetzt werden können. Weiterhin ist beispielsweise auch der Einsatz von magensaftresistenten Filmen möglich. Der Gewichtsanteil der Filmhülle bezogen auf die fertige Tablette liegt im üblichen Bereich von 0,3 - 3,0 Gew.-%, vorzugsweise von 0,8 - 1,2 Gew.%. Als Filmbildner kommen übliche Filmbildner, wie beispielsweise Ethylcellulose, Poly-(methylmethacrylat)-Derivate (Eudragit®) , aber auch lösliche Cellulosederivate wie Methylhydroxypropylcellulose und Cellulosederivate zur Ausbildung magensaftresistenter Filme, wie Cellulose-acetatphthalat oder Methylhydroxypropylcellulosephthalat in Frage. Bevorzugt wird Ethylcellulose verwendet. Durch den gebildeten Film kann die Auflösung des Wirkstoffs verzögert werden. Als übliche Hilfsstoffe können in der Filmhülle Weichmacher, Porenbildner und Pigment enthalten sein.

Die erfindungsgemäße pharmazeutische Zusammensetzung kann auch zur Herstellung von komprimierten Kapselfüllmassen verwendet werden. Diese Komprimate bzw. kompaktierten Granulate können dann in handelsübliche Kapseln mittels geeigneter Vorrichtungen gefüllt werden. Im Vergleich zu den sonst üblichen Metformin-haltigen Kapselfüllmassen haben diese kompaktierten Granulate bei gleichem Wirkstoffgehalt bzw. gleicher Dosierung den Vorteil, daß aufgrund ihres geringeren Volumens kleinere Kapseln verwendet werden können, die leichter von dem Patienten geschluckt werden können.

Die erfindungsgemäßen pharmazeutischen Darreichungsformen, wie z.B. Tabletten, enthalten - neben dem Wirkstoff, dessen Anteil an der Darreichungsform im Bereich

von 70 - 95 Gew.-% liegen kann, (beispielsweise werden 850 mg der Wirkstoffes im Fall von Retardtabletten bevorzugt eingesetzt) und dem Retardierungsmittel - vorzugsweise 2 - 10 Gew.-% Bindemittel, bis zu 2 Gew.-%, vorzugsweise 0,1 - 0,3 Gew.-% Fließregulierungsmittel und bis zu 2 Gew.-%, vorzugsweise 0,4 - 1,1 Gew.-% Schmiermittel, jeweils bezogen auf das Gesamtgewicht der tablettierfertigen Masse bzw. des Tablettenkerns. Das Gewicht eines Tablettenkern liegt in der Regel zwischen 200 und 1300 mg, vorzugsweise im Bereich von weniger als 1200 mg, insbesondere von etwa 500 - 1000 mg. Als Fließregulierungsmittel kommen für die erfindungsgemäße Tablette übliche Mittel wie zum Beispiel kolloidales Siliciumdioxid in Frage. Als Schmiermittel sind beispielsweise Talkum oder Stearinsäure bzw. deren Alkali- oder Erdalkalisalze, insbesondere Magnesiumstearat, geeignet. Als Bindemittel können beispielsweise Cellulosederivate, speziell Alkyl- und Hydroxyalkyl-Cellulosen, insbesondere Methylcellulose, Hydroxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Methylhydroxyethylcellulose, Methylhydroxypropylcellulose, Natriumcarboxymethylcellulose u.a., Dextrine, Stärken, speziell lösliche Stärken, andere Polymere auf Kohlenhydratbasis wie z.B. Galaktomannane, natürliche Gummen wie Gummi arabicum, Traganth, Sterculia, Acacia u.a., Xanthan, Alginate, Polyacrylsäure, Polyvinylalkohol und Polyvinylpyrrolidon eingesetzt werden. Bevorzugt wird Polyvinylpyrrolidon verwendet.

Die erfindungsgemäßen pharmazeutischen Darreichungsformen, wie z.B. Tabletten, werden hergestellt, indem man den Wirkstoff, das Retardierungsmittel oder einen Teil des Retardierungsmittels und gegebenenfalls weitere Hilfsstoffe trocken miteinander vermischt, mit Wasser oder einer wäßrigen Lösung eines Bindemittels feucht granuliert, die tablettierfertige Masse bis zu einer gewünschten Restfeuchte trocknet und danach gegebenenfalls den anderen Teil des Retardierungsmittels oder andere pharmazeutische Hilfsstoffe dem Granulat zumischt, so daß in dem letzten Verfahrensschritt eine Restfeuchte in der pharmazeutischen Zusammensetzung von 0,5 -3 Gew.-% erzielt wird. Die Bestimmung der Restfeuchte erfolgt nach bekannten analytischen Methoden der Aquametrie, beispielsweise durch die Bestimmung des Wassergehaltes mit Hilfe des Karl-Fischer-Reagenzes, oder anderen alternativen Bestimmungsverfahren. Bei der Feuchtgranulation kann auch ein Teil des Wirkstoffes, die verwendeten Hilfsstoffe sowie das Retardierungsmittel ganz oder teilweise in Wasser gelöst oder suspendiert vorliegen. Gegebenenfalls können auch mit Wasser mischbare organische Lösungsmittel, wie beispielsweise Aceton oder niedere Alkohole, wie Methanol oder Ethanol zugesetzt werden.

Die Einstellung der Restfeuchte erfolgt zweckmäßigerweise im Rahmen einer Trocknung im Wirbelschichtverfahren, wobei das feuchte Granulat so lange getrocknet wird, bis die gemessene Feuchtigkeit in der Abluft den zuvor im Rahmen einer Kalibrierung zur Restfeuchte im Trocknungsgut ermittelten Wert erreicht hat. Die so hergestellte Zusammensetzung wird anschließend in üblicher Weise zu pharmazeutischen Darreichungsformen verarbeitet und beispielsweise zu Tabletten verpreßt. Die Tabletten können mit üblichen Überzugsverfahren mit einem Film überzogen werden. Es wurde gefunden, daß die mit Hilfe des Hydrokolloidbildners eingestellte Restfeuchte von 0,5 - 3 Gew.-% gewährleistet , daß die tablettierfertige Masse über den gesamten, zur Herstellung großer Tabletten notwendigen Preßkraftbereich ohne Deckeln komprimierbar ist.

Der Wirkstoff kann ganz oder teilweise mit dem zur Retardierung eingesetzten Hydrokolloidbildner zu einem Granulat verarbeitet werden oder der Hydrokolloidbildner wird vollständig einem Hydrokolloidbildner-freien Granulat nach dessen Herstellung zugemischt. Eine zusätzlich bessere Tablettierbarkeit wird jedoch erreicht, wenn der Hydrokolloidbildner oder ein Teil davon mit dem Wirkstoff granuliert wird.

Das Überziehen der Tablette erfolgt nach üblichen Verfahren wie z. B. dem Dragierkessel- oder Wirbelbettverfahren.

Die erfindungsgemäßen retardierten Tabletten setzen Metformin über einen Zeitraum von 0,5 - 10 Stunden, vorzugsweise über 4 Stunden, kontrolliert frei (Abb. 1). Das Gewicht der Tabletten liegt dadurch, daß durch die Verwendung des Hydrokolloidbildners keine großen Mengen zusätzlicher Hilfsstoffe, insbesondere keine Feuchthaltemittel, wie z.B. Gycerol oder Sorbitol, notwendig sind, bei maximal 1200 mg, vorzugsweise unter 1000 mg.

Nachfolgend soll die Erfindung durch Ausführungsbeispiele verdeutlicht werden, ohne sie darauf einzuschränken.

Bei den folgenden Beispielen 1 - 6 wurde die Restfeuchte auf den erfindungsgemäßen Bereich eingestellt, bevor die pharmazeutische Zusammensetzung in Form einer preßfertigen Masse zu Tabletten verpreßt wurde. In den Beispielen 7 und 8 wurde die Restfeuchte auf einen Wert von weniger als 0,5 Gew.-% eingestellt. In diesen beiden Fällen mußte die Tablettierung aufgrund der hohen Verluste durch Deckeln abgebrochen werden.

Beispiel 1:

Hydrokolloidbildner: Methylhydroxypropylcellulose(MHPC). Der MHPC-Anteil kann variiert werden, z.B. von 40 - 95 mg.

Restfeuchte: 2.1 %

Bestandteile	Tablette [mg]	preßfertige Masse [kg/1 Mio St.]
Kern:		
Metformin-Hydrochlorid	850,00	850,00
Methylhydroxypropylcellulose	60,00	60,00
Polyvidon	38,00	38,00
Magnesiumstearat	5,00	5,00
Kern gesamt:	953,00	953,00
Filmhülle:		
Methylhydroxypropylcellulose	20,00	20,00
Ethylcellulose	12,00	12,00
Macrogol	4,00	4,00
Titandioxid	4,00	4,00
Hülle gesamt:	40,00	40,00
Filmtablette gesamt:	993,00	993,00

Herstellung :

Die Herstellung des Granulats für eine Menge von etwa 1 Million Tabletten erfolgt in fünf Teilansätzen. Für jeden der fünf Teilansätze werden 170 kg Metformin-Hydrochlorid und 12 kg Methylhydroxypropylcellulose trocken miteinander gemischt und mit einer 10%igen wässrigen Bindemittellösung von Polyvidon in einem Mischer feucht granuliert. Danach wird das Granulat in einem Wirbelschichtgranulator getrocknet, bis es eine ausreichende Restfeuchte besitzt. Die fünf Teilansätze werden vereinigt und mit 5 kg Magnesiumstearat gemischt. Die preßfertige Masse wird tablettiert. Die Tablettenkerne werden im Dragierkessel mit dem Film beschriebener Zusammensetzung überzogen.

Bei der aufgeführten Rezeptur wird die Restfeuchte auf 2,1 % eingestellt. Die Tablettierung verläuft entsprechend problemlos, d.h. eine Deckeln der hergestellten Tablettenmasse kann nicht festgestellt werden.

Beispiel 2:

Hydrokolloidbildner: Hydroxyethylcellulose

Restfeuchte: 2,0 %

Bestandteile	Tablette [mg]	preßfertige Masse [kg/1 Mio St.]
Kern:		
Metformin-Hydrochlorid	850,00	850,00
Hydroxyethylcellulose	70,00	70,00
Polyvidon	40,00	40,00
Magnesiumstearat	5,00	5,00
Kern gesamt:	965,00	965,00
Filmhülle:		
Methylhydroxypropylcellulose	5,00	5,00
Lactose	5,00	5,00
Ethylcellulose	10,00	10,
Macrogol	3,00	3,00
Titandioxid	3,00	3,00
Hülle gesamt:	26,00	26,00
Filmtablette gesamt:	991,00	991,00

Herstellung des Granulates und Weiterverarbeitung erfolgt analog zu Beispiel 1; die Tablettierung verläuft entsprechend problemlos.

Beispiel 3:

Hydrokolloidbildner: Natriumcarboxymethylcellulose

Restfeuchte: 2,1 %

Bestandteile	Tablette [mg]	preßfertige Masse [kg/1 Mio St]
Kern:		
Metformin-Hydrochlorid	850,00	850,00
Natriumcarboxymethylcellulose	80,00	80,00
Polyvidon	35,00	35,00
Magnesiumstearat	5,00	5,00
Kern gesamt:	970,00	970,00
Filmhülle:		
Methylhydroxypropylcellulose	5,00	5,00
Ethylcellulose	10,00	10,00
Macrogol	4,00	4,00
Titandioxid	3,00	3,00
Hülle gesamt:	22,00	22,00
Filmtablette gesamt:	992,00	992,00

Herstellung des Granulats und Weiterverarbeitung erfolgt analog Beispiel 1; die Tablettierung verläuft entsprechend problemlos.

Beispiel 4:

Hydrokolloidbildner: Polyacrylsäure
Restfeuchte: 2,8 %

Bestandteile	Tablette [mg]	preßfertige Masse [kg/1 Mio St]
Kern:		
Metformin-Hydrochlorid	850,00	850,00
Polyacrylsäure	60,00	60,00
Methylhydroxypopylcellulose	30,00	30,00
Magnesiumstearat	5,00	5,00
Kern gesamt:	945,00	945,00
Filmhülle:		
Methylhydroxypropylcellulose	10,00	10,00
Ethylcellulose	10,00	10,00
Macrogol	3,00	3,00
Titandioxid	3,00	3,00
Hülle gesamt:	26,00	26,00
Filmtablette gesamt:	971,00	971,00

Herstellung und Weiterverarbeitung des Granulats erfolgt analog zu Beispiel 1. Abweichend dient hier Methylhydroxypropylcellulose als Bindemittel. Die Tablettierung erfolgt problemlos.

Beispiel 5:

Hydrokolloidbildner: Hydroxypropylcellulose
Restfeuchte: 1.95 %

Bestandteile		Tablette [mg]	preßfertige Masse [kg/1 Mio St]
Kern:			
Metformin-Hydrochlorid		850,00	850,00
Hydroxypropylcellulose		60,00	60,00
Polyvidon		40,00	40,00
Magnesiumstearat		5,00	5,00
	Kern gesamt:	955,00	955,00
Filmhülle:			
Poly(ethylacrylat-methylmethacrylat)-Dispersion 30%		6,00*	6,00*
Talk		1,20	1,20
Antischaummittel		0,07	0,07
	Hülle gesamt:	7,27	7,27
	Filmtablette gesamt:	962,270	962,270

*Mengenangabe bezogen auf die Trockensubstanz

Herstellung und Weiterverarbeitung des Granulats erfolgt analog zu Beispiel 1. Abweichend wird hier der Hydrokolloidbildner Hydroxypropylcellulose nicht mitgranuliert sondern dem fertigen Granulat trocken zugemischt.

Beispiel 6:

Hydrokolloidbildner: Methylhydroxypropylcellulose
Restfeuchte: 2,0 %

Im folgenden Beispiel wird auf die Verwendung eines zusätzlichen Bindemittels ganz verzichtet, die eingesetzte Methylhydroxypropylcellulose übernimmt gleichzeitig die Funktion von Binde- und Retardierungsmittel.

Bestandteile	Tablette [mg]	preßfertige Masse [kg/1 Mio St.]
Kern:		
Metformin-Hydrochlorid	850,00	850,00
Methylhydroxypropylcellulose	100,00	100,00
Magnesiumstearat	5,00	5,00
Kern gesamt:	955,00	955,00
Filmhülle:		
Methylhydroxypropylcellulose	20,00	20,00
Ethylcellulose	12,00	12,00
Macrogol	4,00	4,00
Titandioxid	4,00	4,00
Hülle gesamt:	40,00	40,00
Filmtablette gesamt:	995,00	995,00

Herstellung:
Die Herstellung des Granulats erfolgt in 5 Teilansätzen. Für jeden der fünf Teilansätze werden 170 kg des Wirkstoffs Metformin-Hydrochlorid mit 18 kg Methylhydroxypropylcellulose im Wirbelschichtgranulierer vorgelegt. 2 kg Mehylhydroxypropylcellulose werden in 50 l Wasser gelöst. Die trockene Mischung wird mit der Bindemittellösung im Wirbelschichtgranulierer granuliert und anschließend getrocknet. Die fünf Teilansätze werden vereinigt und mit 5 kg Magnesiumstearat gemischt. Diese preßfertige Masse wird tablettiert. Auf die Tablettenkerne wird im Dragierkessel der Film beschriebener Zusammensetzung aufgetragen.

Beispiel 7

Hydrokolloidbildner: Methylhydroxypropylcellulose
Restfeuchte: 0,49 %

Bei der untenstehenden Rezeptur wurde eine Feuchte von 0,49 % erhalten. Aufgrund des zu hohen Verlustes durch Deckeln mußte die Tablettierung abgebrochen werden.

Bestandteile		Tablette [mg]
Kern:		
Metformin-Hydrochlorid		850,00
Methylhydroxypropylcellulose		40,00
Polyvidon		38,00
Magnesiumstearat		5,00
	Kern gesamt:	953,00
Filmhülle:		
Methylhydroxypropylcellulose		20,00
Ethylcellulose		12,00
Macrogol		4,00
Titandioxid		4,00
	Hülle gesamt:	40,00
	Filmtablette gesamt:	993,00

Beispiel 8

Hydrokolloidbildner: Gelatine
Restfeuchte: 0,48 %

Bei der untenstehenden Rezeptur wurde eine Feuchte von 0,48 % erhalten. Aufgrund des zu hohen Verlustes durch Deckeln mußte die Tablettierung abgebrochen werden.

Bestandteile		[mg]
Kern:		
Metformin-Hydrochlorid		850,00
Lactose		70,00
Gelatine		40,00
Siliciumdioxid, hochdispers		2,00
Magnesiumstearat		2,50
	Kern gesamt:	964,50
Filmhülle:		
Methylhydroxypropylcellulose		10,00
Ethylcellulose		9,00
Diethylphthalat		3,00
Titandioxid		3,00
	Hülle gesamt:	25,00
	Filmtablette gesamt	989,5

Patentansprüche

1. Pharmazeutische Zusammensetzung enthaltend Metformin als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel sowie gegebenenfalls pharmazeutisch übliche Hilfsstoffe, wobei die Restfeuchte in der pharmazeutischen Zusammensetzung 0,5 - 3 Gew.-% beträgt.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoffgehalt von Metformin mindestens 70 % beträgt.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Menge des Hydrokolloidbildners 4 - 15 Gew.-% beträgt.

4. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 - 3, dadurch gekennzeichnet, daß der Hydrokolloidbildner ausgewählt ist aus der Gruppe bestehend aus Cellulosederivaten, Dextrinen, Stärken, Polymeren auf Kohlenhydratbasis, natürliche Gummen, Xanthan, Alginate, Gelatine, Polyacrylsäure, Polyvinylalkohol und Polyvinylpyrrolidon.

5. Pharmazeutische Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß der Hydrokolloidbildner ein Cellulosederivat ist, insbesondere eine Alkyl- oder Hydroxyalkylcellulose.

6. Pharmazeutische Zusammensetzung nach Anspruch 5, dadurch gekennzeichnet, daß der Hydrokolloidbildner ausgewählt ist aus Methylcellulose, Hydroxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Methylhydroxyethylcellulose, Methylhydroxypropylcellulose oder Natriumcarboxymethylcellulose.

7. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 - 6 enthaltend 3 - 5 Gew.% Bindemittel, bis zu 2 Gew.% Fließregulierungsmittel und bis zu 2 Gew.% Schmiermittel.

8. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 - 6 zur Herstellung von komprimierten festen pharmazeutischen Darreichungsformen, insbesondere Tabletten oder Komprimaten zur Abfüllung in Kapseln.

9. Pharmazeutische Darreichungsform in Form von Tabletten oder Komprimaten zur Abfüllung in Kapseln enthaltend Metformin als Wirkstoff und einen Hydro-

kolloidbildner als Retardierungsmittel mit einer Restfeuchte von 0,5 - 3 Gew.-% bezogen auf das Gewicht des Tablettenkerns oder der Kapselfüllmasse.

10. Pharmazeutische Darreichungsform nach Anspruch 9 in Form einer Tablette mit einem Endgewicht unter 1300 mg.

11. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen enthaltend Metformin als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel sowie gegebenenfalls weitere pharmazeutisch übliche Hilfsstoffe, dadurch gekennzeichnet, daß man den Wirkstoff und das Retardierungsmittel oder ein Teil davon mit einem wäßrigen, gegebenenfalls bindemittelhaltigen Lösungsmittel granuliert, gegebenenfalls den anderen Teil des Retardierungsmittels oder andere pharmazeutisch übliche Hilfsmittel dem Granulat zumischt, und anschließend das Granulat bis zu einer Restfeuchte von 0,5 - 3 Gew.% trocknet.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß das Granulat zu Tabletten verpreßt wird, die anschließend gegebenenfalls mit einer Filmhülle überzogen werden.

13. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß das Granulat kompaktiert wird und in Kapseln abgefüllt wird.

14. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß als Hydrokolloidbildner Methylhydroxypropylcellulose eingesetzt wird.

15. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß man zur Herstellung des Granulats bis zu 2 Gew.-% Fließregulierungsmittel, bis zu 2 Gew.-% Schmiermittel und bis zu 5 Gew.-% Bindemittel einsetzt, bezogen auf die fertige pharmazeutische Zusammensetzung.

16. Verwendung von pharmazeutischen Zusammensetzungen nach einem der Ansprüche 1 - 8 zur Herstellung von komprimierten pharmazeutischen Darreichungsformen, insbesondere von Tabletten oder Komprimaten zur Abfüllung in Kapseln.

17. Verfahren zur Herstellung eines leicht komprimierbaren pharmazeutischen Granulates enthaltend Metformin als Wirkstoff und einen Hydrokolloidbildner als Retardierungsmittel, dadurch gekennzeichnet, daß das Granulat vor der Komprimierung auf eine Restfeuchte von 0,5 - 3 Gew.-% getrocknet wird.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 95/03610

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/155 A61K9/20

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 283 369 (LIPHA,LYONNAISE INDUSTRIELLE PHARMACEUTIQUE,FR) 21 September 1988 see claims see examples I,III	1-4,8-10
A	US,A,3 621 097 (J.F.SCOTT) 16 November 1971 see claims 1-3 see examples 1,2,4	1-4,8,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1995	04. 01. 96

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 95/03610

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-283369	21-09-88	FR-A-	2611500	09-09-88
		AU-B-	610134	16-05-91
		AU-B-	1272788	08-09-88
		CA-A-	1328606	19-04-94
		DE-D-	3886075	20-01-94
		DE-T-	3886075	14-04-94
		DK-B-	169713	23-01-95
		JP-A-	63230628	27-09-88
		ZA-A-	8801540	26-08-88
US-A-3621097	16-11-71	NONE		

INTERNATIONALER RECHERCHENBERICHT

Int ionales Aktenzeichen
PCT/EP 95/03610

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K31/155 A61K9/20

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP,A,0 283 369 (LIPHA,LYONNAISE INDUSTRIELLE PHARMACEUTIQUE,FR) 21.September 1988 siehe Ansprüche siehe Beispiele I,III	1-4,8-10
A	US,A,3 621 097 (J.F.SCOTT) 16.November 1971 siehe Ansprüche 1-3 siehe Beispiele 1,2,4	1-4,8,11

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ X Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
15.Dezember 1995	04.01.96

Name und Postanschrift der Internationale Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scarponi, U

1

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlich.. gen, die zur selben Patentfamilie gehören

Inv onales Aktenzeichen
PCT/EP 95/03610

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A-283369	21-09-88	FR-A-	2611500	09-09-88
		AU-B-	610134	16-05-91
		AU-B-	1272788	08-09-88
		CA-A-	1328606	19-04-94
		DE-D-	3886075	20-01-94
		DE-T-	3886075	14-04-94
		DK-B-	169713	23-01-95
		JP-A-	63230628	27-09-88
		ZA-A-	8801540	26-08-88
US-A-3621097	16-11-71	KEINE		

CLIFFORD M. DAVIDSON
LESLYE B. DAVIDSON
CARY S. KAPPEL
WILLIAM C. GEHRIS
MOREY B. WILDES
ROBERT J. PARADISO
ERIK R. SWANSON****
THOMAS P. CANTY****

FELIX L. D'ARIENZO, JR.

DAVID G. KNASIAK
RICHARD V. ZANZALARI*
BENJAMIN S. DIMARCO*
FRANKLIN S. ABRAMS
MICHELLE L. BLAT**
HEIDI M. STRUSE***

DDK
INTELLECTUAL PROPERTY
NEW YORK | FRANKFURT

NEW YORK
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018
T. 212-736-1940
F. 212-736-2427
DDK@DDKPATENT.COM

FRANKFURT
DAVIDSON, DAVIDSON & KAPPEL EUROPE, LLC
ARNDTSTRASSE 11
60325 FRANKFURT AM MAIN, GERMANY
T. +49 (69) 788 088-0
F. +49 (69) 788 088-29
FRANKFURT@DDKPATENT.COM

*ADMITTED IN NEW JERSEY ONLY
**ADMITTED IN CONNECTICUT ONLY
***ADMITTED IN TEXAS & DISTRICT OF COLUMBIA
****DDK EUROPE

FACSIMILE TRANSMITTAL

FROM: Clifford M. Davidson

PAGES: 2 (including cover sheet)

DATE: November 19, 2003

Attorney Docket Nos.: 300.1012

PLEASE DELIVER THE FOLLOWING TO:

Recipients(s): **T. Page** ***Fax Number: 1-703-308-4556***

MESSAGE: Please see attached.

This transmission was sent from fax number (212) 736-2427. If you have any problems with your reception, please telephone the sender at (212) 736-1940 Ext. 231.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper with enclosures are being facsimile transmitted to the Patent and Trademark Office on the date shown below.

David G. Knasiak — 11/19/03 Date

IF THERE ARE ANY PROBLEMS WITH RECEPTION OF THIS FAX, PLEASE CALL OR FAX SENDER TO ADVISE. THANK YOU.

PTOL-413A (05-03)
Approved for use through xx/xx/xxxx. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Applicant Initiated Interview Request Form

Application No.: 09/705,625 First Named Applicant: Xiu Xiu CHENG
Examiner: WARE, Todd Art Unit: 1615 Status of Application: Response to Office Action Filed

Tentative Participants:
(1) Clifford M. Davidson (2) Ted Whitlock
(3) Thurman Page (4)

OFFICIAL
RECEIVED
CENTRAL FAX CENTER
NOV 19 2003

Proposed Date of Interview: 11/20/2003 **Proposed Time:** 2:00 (AM/PM)

Type of Interview Requested:
(1) [ ] Telephonic (2) [X] Personal (3) [ ] Video Conference

Exhibit To Be Shown or Demonstrated: [ ] YES [X] NO
If yes, provide brief description:

Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
(1) 112 rejection			[ ]	[ ]	[ ]
(2) 103 rejections			[ ]	[ ]	[ ]
(3) double patenting rejections			[ ]	[ ]	[ ]
(4) allowable subject matter			[ ]	[ ]	[ ]

[ ] Continuation Sheet Attached

Brief Description of Arguments to be Presented:
Response to Office Action

An interview was conducted on the above-identified application on _____.

NOTE:
This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).
This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible.

(Applicant/Applicant's Representative Signature) (Examiner/SPE Signature)

FORM PTO-1083

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Docket No.: 300.1012
Date: October 14, 2003

1615

In re application: Xiu Xiu Cheng, et al.
Serial No.: 09/705,625
Filed: November 3, 2000
For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

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.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus**	=	0	x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus***	=	0	x $ 42	$		x $ 84	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $140	$		+ $280	$
				TOTAL:	$	OR	TOTAL:	$

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[ ] Also transmitted herewith are:
[ ] Petition for extension under 37 C.F.R. 1.136 (in duplicate)
[ ] Other:

[ ] Check(s) in the amount of **$.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[ ] Petition fee for 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.

Clifford M. Davidson, Reg. No. 32,728
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

David G. Gosnell
Reg No. 45,991

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

Oct. 14, 2003

DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: David G. Gosnell

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

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

October 14, 2003

AMENDMENT UNDER 37 C.F.R. § 1.111

S i r:

Reconsideration of the present application in view of the following amendments and remarks is respectfully requested.

I. INTRODUCTORY COMMENTS

In response to the Office Action mailed on July 14, 2003, please amend the above-referenced application as provided in the section below entitled "AMENDMENTS TO THE CLAIMS."

II. AMENDMENTS TO THE CLAIMS

Claim 1. (currently amended) A method for 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 at least one oral controlled release dosage form comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and an effective amount of a controlled release carrier to control the release of said meformin or pharmaceutically acceptable salt thereof from said dosage form, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration following dinner; and the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for administration of a 2000 mg once-a-day dose of metformin.

Claims 2-3 (cancelled)

Claim 4. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

Claim 5. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.0 hours after the administration.

Claim 6. (cancelled)

Claim 7. (previously presented) The method of claim 1, in which the administration of the at

least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of metformin from about 4.5 to about 13 hours.

Claim 8. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of metformin from about 5.5 to about 10 hours.

Claim 9.(previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form 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 administration.

Claim 10. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form 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.

Claim 11. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form 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.

Claims 12 - 13. (cancelled)

Claim 14. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from 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.

Claim 15. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ that is from at least 90% 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.

Claims 16-17. (cancelled)

Claim 18 (currently amended) The method of claim ~~16~~1, in which the once-a-day dosage of the metformin is about 2000 mg, which is provided by two controlled release dosage forms containing about 1000 mg.

Claims 19 - 21. (cancelled)

Claim 22. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin.

Claims 23 - 25. (cancelled)

Claim 26. (previously presented) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $t_{1/2}$ from 2.8 to 4.4.

Claim 27. (previously presented) The method of claim 1, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

Claim 28. (previously presented) The method of claim 1, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

Claim 29. (previously presented) The method of claim 1, in which the dose of metformin comprises metformin hydrochloride.

Claim 30. (original) The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 1000 mg to about 2500 mg.

Claim 31. (original) The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 2000 mg to about 2500 mg meformin.

Claims 32-34. (cancelled)

Claim 35. (new) The method of claim 1, in which the once-a-day dose of metformin or pharmaceutically acceptable salt thereof is 2000 mg.

Claim 36. (new) The method of claim 1, in which the once-a-day dose of metformin or pharmaceutically acceptable salt thereof is 1000 mg.

Claim 37. (new) The method of claim 1, in which the once-a-day dose of metformin or pharmaceutically acceptable salt thereof is 500 mg.

III. REMARKS

The undersigned gratefully acknowledges the Examiner's indication in the last Office Action that claim 25 would be allowable if rewritten in dependent form, which has been done by virtue of this amendment, without prejudice to applicants pursuing remaining subject matter in continuation applications. It is respectfully submitted that this amendment places the previously deemed allowable subject matter into condition for allowance.

A. Status of the Claims

The Examiner indicated that Claim 25 would be allowable if rewritten in independent from including all of the limitations of the base claim and any intervening claims. Therefore, Claim 1 has been amended to incorporate Claim 25. It is respectfully submitted that no new matter has been added by virtue of this amendment.

Claims 1, 4-5, 7-11, 14-15, 26-31 and 35-37 are pending. Claims 12-13, 19-21, and 23-25 have been cancelled without prejudice by virtue of this amendment. Claims 1 and 18 have been amended without prejudice by virtue of this amendment. The Examiner indicated that Claim 25 would be allowable if rewritten in independent from including all of the limitations of the base claim and any intervening claims. Therefore, Claim 1 has been amended to incorporate Claim 25. It is respectfully submitted that no new matter has been added by virtue of this amendment.

New claims 35 – 37 have been added which are directed to particular dosage strengths to be administered via the method set forth in amended claim 1. Support for these different strengths is found throughout the specification, including page 7 lines 19 – 26; page 8, lines 3-9. Original claims as filed and as pending specifically call for dosage strengths of 1000 and 2000 mg metformin, among other strengths. In this regard, the Examiner is reminded that, as stated in the specification at page 7, lines 4 – 10, "a given plasma level (e.g., C_{max}) of metformin per

specified dose will be directly proportional to other doeses 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." Applicants point out that the previous amendment to claims 22 -25 was intended to clarify that the particular ranges of the claimed pharmacokinetic parameters (i.e., C_{max} and AUC) were directed to the 2000 mg dose, and were not intended to limit the scope of the claims solely to a 2000 mg dosage strength.

B. Claim objection

In the Office Action, claim 18 was objected to as depending from cancelled claim 17. Claim 18 has been amended to depend from claim 1. The Examiner is requested to withdrawal this objection.

C. Rejection of Claim 18 under 35 U.S.C. §112, second paragraph

In the Office Action, claim 18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner notes that claim 18 depends from cancelled claim 17.

In response, claim 18 has been amended to depend from claim 1. Therefore, the Examiner is requested to withdrawal this rejection.

D. Rejections of Claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) over Lewis et al. in combination with Chiao and Drug Facts and Comparisons OR Moeckel et al. in combination with Chiao and Drug Facts and Comparisons

Claims 1, 4-5, 7-15, 18-24, 26-31 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999) OR Moeckel et al (5,955,106; hereafter '106) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999)."

The Examiner states that "it would have been obvious to one skilled in the art at the time of the invention to combine '989 with Chaio and DFC or '106 with Chiao and DFC with the motivation of providing controlled delivery of metformin over a desired period of time to lower blood glucose levels when an individual is in the fed state. Applicant's comments filed 3-4-03, Paper #11, stating that numerous controlled release technologies are well within the knowledge of pharmaceutical formulators having ordinary skill in the art and such pharmaceutical formulators know that controlled release can be manipulated, e.g., by varying the amount of controlled release carrier (among other things), to provide a formulation which upon *in vivo* testing will provide the Tmax range of the present invention (pages 8-9 of response), are also relied upon for supporting the above position.

In view of the amendment to claim 1, incorporating allowable claim 25 of the present application, the Examiner's rejection with respect to Claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999) OR Moeckel et al (5,955,106; hereafter '106) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999) is now moot. The Examiner is respectfully requested to remove this rejection.

E. Rejections of Claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) over Cheng et al. in view of Drug Facts and Comparisons

Claims 1, 4-5, 7-15, 18-24, and 26-31 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (WO 99/47125; hereafter '125) in view of Drug Facts and Comparisons (1999).

The Examiner states that "it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 and lower blood glucose levels accordingly with the motivation of providing controlled

delivery of metformin over a desired period of time and to administer the compositions at dinner or at a fed state with the motivation of regulating sugar levels.

In view of the present amendment, claims 32-34 of the present application have been canceled without prejudice rendering the Examiner's rejection moot. Therefore, the Examiner is respectfully requested to withdraw the rejection of claims 32-34 under 35 U.S.C. §102(b) for the above-referenced application.

In view of the amendment to claim 1, incorporating allowable claim 25 of the present application, the Examiner's rejection with respect to Claims 1, 4-5, 7-15, 18-24, and 26-31 under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (WO 99/47125; hereafter '125) in view of Drug Facts and Comparisons (1999) is now moot. The Examiner is respectfully requested to remove this rejection.

F. Double Patenting Rejections

Claims 1, 4-5, 7-15, and 18-31 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following:

claims 1-29 of U.S. Patent No. 6,099,859;

claims 1-39 of U.S. Patent No. 6,284,275; and

claims 1-4 of U.S. Patent No. of U.S. Patent no. 6,099,862.

In addition claims 1, 4-5, 7-15, and 18-31 were provisionally rejected over claims 1-29 of copending Application No. 09/726,193.

In response, Applicants will consider the filing of Terminal Disclaimers to obviate the double-patenting rejections upon indication from the Examiner that the claims are otherwise allowable.

G. Conclusion

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

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.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

by David G. Conlin
Reg No. 45,991

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

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.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

23280 7590 07/14/2003

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

EXAMINER
WARE, TODD

ART UNIT	PAPER NUMBER
1615	12

DATE MAILED: 07/14/2003

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

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/705,625	Applicant(s) CHENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2001* .

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

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

Disposition of Claims

4)☒ Claim(s) *1, 4-5, 7-15, and 18-31* 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) *1, 4-5, 7-15, 18-24, and 26-31* is/are rejected.

7)☒ Claim(s) *25* 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ 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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of request for extension of time (granted) and amendment/response all filed 3-4-03 is acknowledged. In view of Applicant's comments and the new grounds for rejection, the instant Office Action is non-final. Claims 2-3, 6, 16-17, and 32-34 have been canceled and claims 1, 4-5, 7-15, and 19-29 have been amended as requested. Claims 1, 4-5, 7-15, and 18-31 are pending.

Claim Objections

1. Claim 18 is objected to because of the following informalities: claim 18 depends from canceled claim 17. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. 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.

3. Claim 18 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.

4. Claim 18 depends from canceled claim 17.

Claim Rejections - 35 USC § 103

5. 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.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 4-5, 7-15, 18-24, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999) **OR** Moeckel et al (5,955,106; hereafter '106) in combination with Chiao (Remington, 1995) and further in combination with Drug Facts and Comparisons (1999).

8. '989 and '106 both teach controlled release metformin compositions but do not teach the exact release profile(s) of the instant claims.

9. Chiao is relied upon for teaching manipulation of controlled release formulations in achieving a desired release profile. Such manipulation can occur, for example, by

varying the controlled release carrier, amount of controlled release ingredients, or thickness of coating(s) of controlled release ingredients.

Drug Facts and Comparisons (DFC) is relied upon for teaching delivery of metformin in the presence or absence of food.

10. Accordingly, it would have been obvious to one skilled in the art at the time of the invention to combine '989 with Chiao and DFC or '106 with Chiao and DFC with the motivation of providing controlled delivery of metformin over a desired period of time to lower blood glucose levels when an individual is in the fed state. Applicant's comments filed 3-4-03, Paper # 11, stating that numerous controlled release technologies are well within the knowledge of pharmaceutical formulators having ordinary skill in the art and such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g. by varying the amount of controlled release carrier (among other things), to provide a formulation which upon *in* vivo testing will provide the T_{max} range of the present invention (pages 8-9 of response), are also relied upon for supporting the above position.

11. Claims 1, 4-5, 7-15, 18-24, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (WO 99/47125; hereafter '125) in view of Drug Facts and Comparisons (1999).

12. '125 teaches controlled release metformin compositions but does teach the exact release profile(s) of the instant claims. In addition, '125 discloses a semi-permeable membrane coating surrounding the core. '125 incorporates by reference US Patent No.

3,845,770 (hereafter '770) to further describe the passageway and therefore drug release from the formulations taught therein. Briefly, '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67).

13. Drug Facts and Comparisons (DFC) is relied upon for teaching delivery of metformin in the presence or absence of food.

14. Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 and lower blood glucose levels accordingly with the motivation of providing controlled delivery of metformin over a desired period of time and to administer the compositions at dinner or at a fed state with the motivation of regulating sugar levels.

Double Patenting

15. 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. See *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) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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).

16. Claims 1, 4-5, 7-15, and 18-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859. '859 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

17. Claims 1, 4-5, 7-15, and 18-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275. '275 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the

release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

18. Claims 1, 4-5, 7-15, and 18-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862. '862 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

19. Claims 1, 4-5, 7-15, and 18-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/726,193. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are within the scope (species) of the claims of Application No. 09/726,193 (genus).

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

Allowable Subject Matter

20. Claim 25 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

tw
July 10, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice of References Cited	Application/Control No. 09/705,625	Applicant(s)/Patent Under Reexamination CHENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-3,845,770	11-1974	Theeuwes et al.	424/427
*	B	US-5,955,106	09-1999	Moeckel et al.	424/464
*	C	US-6,099,859	08-2000	Cheng et al.	424/464
*	D	US-6,099,862	08-2000	Chen et al.	424/473
*	E	US-6,284,275	09-2001	Chen et al.	424/473
	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	WO 9947125 A1	09-1999	World Intellect	CHENG et al.	A61K 09/20
*	O	WO 0028989 A1	05-2000	World Intellect	Lewis et al	A61K 31/353
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Chiao, C. Sustained-Release Drug Delivery Systems Remington: the Science and Practice of Pharmacy, 1995, Mack Publishing Company, Easton, PA Pages 1660-1669.
	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.

300.1012

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

February 28, 2003

S i r:

In accordance with Applicant's duty of disclosure under 37 C.F.R.§1.56 and the provisions of 37 C.F.R. §§ 1.97 and 1.98, Applicants hereby make of record the documents listed on the accompanying Form PTO-1449 for consideration by the Examiner in connection with the examination of the above-identified patent application.

Applicants note that reference AM is being submitted in an envelope labeled "PROPRIETARY MATERIAL NOT OPEN TO PUBLIC. TO BE OPENED ONLY BY EXAMINER OR OTHER AUTHORIZED U.S. PATENT AND TRADEMARK OFFICE EMPLOYEE." as this material in the envelope is considered proprietary and is being submitted for consideration under MPEP §724 (8th Edition).

The biostudy (which resulted in the data submitted as reference AM) was performed using formulations prepared in accordance with U.S. Patent No. 6,099,859. 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 (*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.

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 fee is due, the Examiner is authorized to charge said fee to Attorney Deposit Account No. 50-0552.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1012	SERIAL NO.: 09/705,625
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Xiu Xiu CHENG, et al.	
		FILING DATE: November 3, 2000	GROUP: 1615

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	6 4 7 5 5 2 1	11/05/2002	Timmins et al.	424	469	Sep. 16, 1999
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AH							
	AI							
	AJ							
	AK							
	AL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AM	Andrx Pilot Biostudy Data (20 pages)
	AN	
	AO	
	AP	
	AQ	
	AR	
	AS	

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.

FORM PTO-1083

Docket No.: 300.1012
Date: February 28, 2003

ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

In re application: **Xiu Xiu Cheng, et al.**
Serial No.: **09/705,625**
Filed: **November 3, 2000**
For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

S i r:

Transmitted herewith is an **Information Disclosure Statement** 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)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus** =		x0$ 9	$			x $ 18	$
INDEP. CLAIMS	* Minus*** =		x0$ 40	$			x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			+$135	$			+ $270	$
				TOTAL: $		OR	TOTAL:	$

[X] Also transmitted herewith are:
[ ] Petition for extension under 37 C.F.R. 1.136
[X] Other: **Form PTO 1449 and accompanying reference; and Material Submitted for consideration under MPEP § 724**

[X] Check(s) in the amount of **$180.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[ ] Petition fee for extension under 37 C.F.R. 1.136
[X] Other: **Fee for submission of Information Disclosure Statement**

[X] The Assistant 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.

Clifford M. Davidson, Reg. No. 32,728
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

FORM PTO-1083

Docket No.: **300.1012**
Date: **February 24, 2003**

ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

$1615

In re application: **Xiu Xiu Cheng, et al.**
Serial No.: **09/705,625**
Filed: **November 3, 2000**
For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

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.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus** =		x0$ 9	$			x $ 18	$
INDEP. CLAIMS	* Minus*** =		x0$ 40	$			x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				$			+ $270	$
				TOTAL: $		OR	TOTAL: $	

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

[X] Check(s) in the amount of **$110.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for extension under 37 C.F.R. 1.136
[ ] Other:

[X] The Assistant 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.

Clifford M. Davidson, Reg. No. 32,728
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 the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on February 24, 2003.

DAVIDSON, DAVIDSON & KAPPEL, LLC
BY:

#11B

300.012

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

February 24, 2003

AMENDMENT UNDER 37 C.F.R. § 1.111

S i r:

In response to the Office Action mailed on October 22, 2002, Applicants respectfully request reconsideration of the application in view of the following amendments and remarks.

IN THE CLAIMS

Please **cancel** claims 2-3, 6, 16-17, and 32-34.

Please **amend** the claims as follows:

1. (Twice Amended) A method for 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 at least one oral controlled release dosage form comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and an effective amount of a controlled release carrier to control the release of said meformin or pharmaceutically acceptable salt thereof from said dosage form, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration following dinner.

B2

4. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin ~~at from 5.5 to 7.0 hours~~ after the administration.

B3

7. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of metformin from about 4.5 to about 13 hours.

8. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of metformin from about 5.5 to about 10 hours.

9.(Amended) The method of claim 1, in which the administration of the at least one metformin dosage form 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 administration.

10. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form 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.

11. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form 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.

12. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, for administration of a 2000 mg once-a day dose of metformin.

13. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

14. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from 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.

15. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ that is from at least 90% 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.

16. (Amended) The method of claim 1, in which the once-a-day dose of the metformin is administered at dinner.

19. (Amended) The method of claim 1, in which the administration of the at least one

metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, for administration of a 2000 mg once-a-day dose of metformin.

20. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, for administration of a 2000 mg once-a-day dose of metformin.

21. (Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, for administration of a 2000 mg once-a-day dose of metformin.

22. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin.

23. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

24. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24}$ of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

25. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24}$ of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean $AUC_{0\text{-}24}$ of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14^{th} day of administration, for administration of a 2000 mg once-a-day dose of metformin.

B5 cont

26. (Twice Amended) The method of claim 1, in which the administration of the at least one metformin dosage form provides a mean $t_{1/2}$ from 2.8 to 4.4.

B6

27. (Amended) The method of claim 1, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. (Amended) The method of claim 1, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. (Amended) The method of claim 1, in which the dose of metformin comprises metformin hydrochloride.

REMARKS

Reconsideration of the present application is respectfully requested. An early and favorable action on the merits is earnestly solicited.

I. Status of the Claims

Claims 1, 4-5, 7-15, and 18-31 are pending; claims 2-3, 6, 16-17, and 32-34 have been cancelled without prejudice; and claims 1, 4-5, 7-15, and 19-29 have been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Rejection of Claims 1-31 under 35 U.S.C. §112, first paragraph

In the Office Action, claims 1-31 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "[t]he instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation." The Examiner directs the Applicants attention to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and the eight factors discussed therein when assessing if a disclosure would have required undue experimentation.

The Examiner notes that "these examples are neither exhaustive, nor define the class of compound required," and that "[t]he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." The Examiner further states that "the instant claims read on all antihyperglycemic drug compositions where the maximum plasma concentration occurs from 5.5-7.5 hours after administration, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

In response and in order to advance the prosecution of the present application, claim 1 has been amended without prejudice to recite "metformin" in place of "antihyperglycemic drug." The claims of the present application are clearly enabled for metformin or a pharmaceutically acceptable salt thereof, and as amended, the present claims do not "read on all antihyperglycemic compositions".

In any event, Applicants are not required to exemplify every formulation which would be encompassed by the claim and it would be tremendously costly, inefficient and perhaps unethical to require manufacturing and testing of alternative formulations as apparently deemed necessary by the Examiner in the last Office Action. At the time the present application was filed, there were numerous controlled release technologies in the art, and testing for drug-plasma levels is routine in clinical studies.

Therefore, it is respectfully submitted that once the T_{max} range which provides for a useful dosage form has been established, other controlled release technologies known in the art can be manipulated and tested to achieve this T_{max} range without undue experimentation as discussed below.

A. The Test for Enablement

It is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 8 USPQ2d at 1046 (1989). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 USPQ2d at 1404 (*citations omitted*). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id. (Emphasis added)*. The very nature of pharmaceuticals requires both formulation work and clinical (in-vivo) evaluation, and therefore giving due regard for the nature of the invention, the amount of experimentation needed to prepare a suitable controlled release formulation using a technology other than that exemplified in the specification does not amount to undue experimentation.

B. Dosage Forms and Plasma Profile of the Present Invention

In the Office Action the Examiner states that "Applicant fails to set forth the criteria that defines the dosage form or steps in the production of the composition that results in the dosage form having the instant claimed plasma profile," and that "Applicant fails to provide information allowing the skilled artisan to ascertain the plasma profile without undue experimentation."

The invention as claimed is directed to a method of treatment wherein a maximum plasma concentration is obtained at 5.5 to 7.5 hours after administration, irrespective of the particular technology employed in the controlled release dosage form. Certain representative examples of these formulations are provided in the present application, and it is explained have stated in the specification that a number of controlled release technologies are useful in order to obtain the claimed pharmacokinetic parameters of the present invention.

Examples 1-3 of the present application which are directed to a tablet formulation containing metformin HCl, a seal coating, and a sustained release coating. Example 3 of the present application described clinical studies which were conducted to evaluate formulations prepared in accordance with Examples 1-3, which together with the specification enable the claimed methods of lowering blood glucose levels in human patients with oral controlled release dosage forms of metformin or a pharmaceutically salt thereof which provide the T_{max} values of the present invention. The Examiner's attention is respectfully directed to page 19, line 21 to page 20, line 14 which states the following:

> 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 addition, at the time the application was filed, numerous controlled release technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. Such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g., by varying the amount of controlled release carrier (among other things), to provide a formulation which upon in-vivo testing will provide the T_{max} range of the present invention. This fact is supported, e.g., by a simple review of patents discussed in the specification concerning formulation technologies, which patents provide ranges of ingredients. These ranges represent the acknowledgement of those skilled in the art that a certain amount of experimentation is considered to be necessary to manipulate a controlled release technology to

obtain a desired release pattern of the drug. Such release patterns are demonstrated by the (well-known) use of in-vitro dissolution testing, which is considered by pharmaceutical formulators of ordinary skill in the art to provide guidance as to which particular formulations might provide the desired in-vivo performance.

Next, it is well known to those of ordinary skill in the art that upon formulating prospective products which might be useful in humans, in-vivo clinical studies must be conducted to determine whether the prospective product actually provides the desired in-vivo performance. Plasma profiles are routinely obtained during clinical trials and in particular during phase I-III studies as indicated in J.T. Cartensen, Pharmaceutical Principles of Solid Dosage Forms, 1993 (attached herewith).

It is respectfully submitted that none of the above steps, either separately or collectively, rise to the level of undue experimentation. Once the goal has been identified and has been attained (as in the present exemplified formulations set forth in the specification), it is respectfully submitted that a pharmaceutical formulator of ordinary skill in the art can manufacture prospective dosage forms for evaluation (to determine if they meet the required in-vivo parameters), a clinician of ordinary skill in the art can administer the dosage forms and draw blood at appropriate time intervals, and a pharmacokineticist of ordinary skill in the art can evaluate the in-vivo blood plasma results.

These steps represent a clear pattern followed by every pharmaceutical company in the world. There is no alternative short-cut known which is considered to be acceptable by government regulatory agencies (such as FDA). Since human experiments with pharmaceuticals are generally considered unethical if being done solely for patent purposes, the Examiner appears to be requiring this Applicant to conduct studies that are unethical, unnecessary and not legally required to support the rightful scope of Applicant's claims. Accordingly, it is earnestly requested that the Examiner remove this basis for rejection.

The Examiner is reminded that Applicants are not required to exemplify every formulation which would be encompassed by the claim. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 84 (CCPA 1970); MPEP 2164.01(b) (8th Edition) ("As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.").

In *Telectronics*, for example, the court found that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *Telectronics,* 8 USPQ2d at 1223 (*citing SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention)).

Therefore, it is respectfully submitted that by virtue of the present application Applicants have disclosed a T_{max} range which provides for a useful dosage form of metformin or a pharmaceutically acceptable salt thereof, and other controlled release technologies known in the art can be manipulated by one of ordinary skill in the art to achieve this T_{max} range without undue experimentation.

C. U.S. Patent No. 6,099,859

In the rejection, the Examiner states that "[i]n the instant case, the provided examples set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859)." However, the Examiner notes that " '859 discloses that the peak plasma profile is approximately 8-12 hours after administration, whereas the instant specification/claims state that the dosage forms, which appear to have the same composition and process of making as '859, have a peak plasma profile of 5.5-7.5 hours."

(1) The specification of '859 states in a preferred embodiment, that peak plasma levels are obtained between 8-12 hours after administration (See column 2, lines 50-55).

(2) In actuality however, 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 an Information Disclosure Statement which will subsequently be hand delivered to the Examiner, the mean T_{max} values for the Examples of the '859 were as follows: Example 1 (fasting) 4.67 hours; Example 2 (fasting) 4.33 hours; Example 2 (fed a.m.) 6.80 hours; Example 3 (fed a.m.) 6.67 hours; Example 3 (Fed p.m.) 9.67 hours. Therefore, the only instance the T_{max} was between 8-12 hours was Example 3 fed in the P.M. (at dinner).

The claims have now been amended to state the "T_{max} of metformin at from 5.5 to 7.5 hours after single dose administration following dinner." The claims as now written are directed to methods and treatments which were never accomplished in the Examples of the '859 patent.

With respect to the Examiner's position that the provided examples of the present application set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859), the Examiner's attention is respectfully directed to the fact that the formulations exemplified and tested in the present application are indeed different as the formulations of the Examples of the present application differ from those of the '859 by having two laser drilled holes, and the method achieved a different result than that reported in the '859 or achieved by clinical testing of Examples 1-3. However, it is respectfully submitted that one skilled in the art would be able to manipulate the processes and formulations of the '859 by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation.

Therefore, in view of the aforementioned, it is respectfully submitted that the formulations of the present invention are different than those of the '859 patent.

D. Conclusion

In the specification, Applicants have provided formulations, methods of making the formulations, and clinical studies of these formulations, that support the limitations (e.g., T_{max} values) recited in the present claims. Further, the prior art is replete with controlled release technology and, as stated in the present application, a number of controlled release technologies can be used to manufacture formulations which provide the results recited in the present claims without undue experimentation. Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. §112 rejection of the pending claims.

III. Rejection of Claims 22-25 under 35 U.S.C. 112, second paragraph

Claims 22-25 were rejected under 35 U.S.C. 112, second paragraph, on the grounds of indefiniteness.

Specifically, the Examiner states that "[r]ecitation of 'based on' in claims 22-25 is indefinite since it is unclear whether Applicant is claiming that the dose of administration for metformin is 'X' mg after an evening meal or whether another dose of metformin provides these limitations. In the event the $AUC_{0\text{-infinity}}$ for a particular dose of metformin is claimed, amendment with 'for administration' is suggested to overcome the instant rejection."

In response and for purposes of advancing the prosecution of the present application, claims 22-25 have been amended without prejudice to recite the term "for" administration rather than "based on" administration, as suggested by the Examiner.

In view of the actions taken, the Examiner is respectfully requested to remove the rejection of claims 22-25 under 33 U.S.C. 112, second paragraph.

IV. Rejection of Claims 32-34 under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125).

Claims 32-34 were rejected under 35 U.S.C. 102(b) "as being anticipated by Cheng et al (WO 99/47125; hereafter '125)". The Examiner states that "'125 discloses controlled release antihyperglycemic dosage form that has the same composition taught by the specification as providing the instant mean fluctuation indexes."

In view of the present amendment, claims 32-34 of the present application have been canceled without prejudice rendering the Examiner's rejection moot. Therefore, the Examiner is respectfully requested to withdraw the rejection of claims 32-34 under 35 U.S.C. §102(b) for the above-referenced application.

V. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

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

An early and favorable action is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 2-3, 6, 16-17, and 32-34 have been cancelled without prejudice.

The claims have been amended as follows:

1. (Twice Amended) A method for 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 at least one oral controlled release dosage form comprising an effective dose of **[at least one suitable antihyperglycemic agent] metformin** or a pharmaceutically acceptable salt thereof and **an effective amount of** a controlled release carrier **to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form**, wherein **following oral administration of a single dose,** the dosage form provides a mean time to maximum plasma concentration (T_{max}) of **[agent] metformin** at from 5.5 to 7.5 hours after administration **following dinner**.

4. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from **[about]** 5.5 to 7.0 hours after the administration.

7. (Amended) The method of claim **[3] 1**, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma

concentration/time curve of **[the drug]** **metformin** from about 4.5 to about 13 hours.

8. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a width at 50% of the height of a mean plasma concentration/time curve of **[the drug]** **metformin** from about 5.5 to about 10 hours.

9.(Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form 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 administration.

10. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form 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.

11. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form 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.

12. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, **for** **[based on]** administration of a 2000 mg once-a day dose of metformin.

13. (Amended) The method of claim **[3]** 1, in which the administration of the at least one metformin dosage form provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, **for** **[based on]** administration of a 2000 mg once-

a-day dose of metformin.

14. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} from at least 80% of the mean AUC_{0-24} 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.

15. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} that is from at least 90% of the mean AUC_{0-24} 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.

19. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 33900 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

20. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 26500 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

21. (Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} from about19800 ng.hr/ml to about 33900 ng.hr/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin.

22. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, **for [based on]** administration of a 1700 mg once-a-day dose of metformin

[after an evening meal].

23. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

24. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

25. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

26. (Twice Amended) The method of claim **[3]** **1**, in which the administration of the at least one metformin dosage form provides a mean **[$T_{1/2}$]** $t_{1/2}$ from 2.8 to 4.4.

27. (Amended) The method of claim **[3]** **1**, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. (Amended) The method of claim **[3]** **1**, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. (Amended) The method of claim **[3]** **1**, in which the dose of metformin comprises metformin hydrochloride.

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

PETITION FOR EXTENSION UNDER 37 CFR 1.136(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

February 24, 2003

Sir:

Applicants petition the Assistant Commissioner for Patents to extend the time for response to the Office Action dated October 22, 2002 for one (1) month from January 22, 2003 to February 24, 2003.

A check in the amount of $110.00 is enclosed to cover the one month extension fee. If it is determined that additional fees are due at this time, the Assistant Commissioner is hereby authorized to charge said fees to Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

23280 7590 10/22/2002

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

EXAMINER	
WARE, TODD	
ART UNIT	**PAPER NUMBER**
1615	9

DATE MAILED: 10/22/2002

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

Office Action Summary	Application N .	Applicant(s)	
	09/705,625	CHENG ET AL.	
	Examiner	Art Unit	
	Todd D Ware	1615	

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 July 2002* .

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

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

Disposition of Claims

4)☒ Claim(s) *1-34* 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) *1-34* 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ 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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of request for extension of time (granted), amendment and terminal disclaimer all filed 7-8-02 is acknowledged. Claims 1, 2, 3, 22, 23, 25, 26 have been amended as requested. Claims 1-34 are pending. Based upon the new grounds for rejection, the instant Office Action is "non-final."

Claim Rejections - 35 USC § 112

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

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

2. Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines the dosage form or steps in the production of the composition that results in the dosage form having the instant claimed plasma profile. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain the plasma profile without undue experimentation. In the instant case, the provided examples set forth dosage forms made according to a process where the dosage forms have the same composition as those of US 6,099,859 ('859). However, '859 discloses that the peak plasma profile is approximately 8-12 hours after administration, whereas the instant specification/claims state that the dosage forms, which appear to have the same composition and process of making as '859, have a peak plasma profile of 5.5-7.5 hours. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all antihyperglycemic drug compositions where the maximum plasma concentration occurs from 5.5-7.5 hours after administration, necessitating an exhaustive search for the embodiments suitable to practice the claimed

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

4. 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.

5. Claims 22-25 are 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.

6. Recitation of "based on" in claims 22-25 is indefinite since it is unclear whether Applicant is claiming that the dose of administration for metformin is "X" mg after an evening meal or whether another dose of metformin provides these limitations. In the event the $AUC_{0\text{-infinity}}$ for a particular dose of metformin is claimed, amendment with "for administration" is suggested to overcome the instant rejection.

Claim Rejections - 35 USC § 102

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

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

8. Claims 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125; hereafter '125).

9. '125 discloses controlled release antihyperglycemic dosage form that has the same composition taught by the specification as providing the instant mean fluctuation indexes.

Response to Arguments

10. Applicant's arguments filed 7-8-02 have been fully considered but they are not persuasive. Applicant argues that the dosage forms of '125 do not disclose the same plasma profiles as in instant claims 1-31, however, the instant claims are not limited to plasma profiles. It is again submitted that the instant dosage forms are the same as those of '125 and that they would have the same mean fluctuation index.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

tw
October 20, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

FORM PTO-1083

Docket No.: 300.1012
Date: July 1, 2002

ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

1615

In re application: **Chih-Ming Chen, et al.**
Serial No.: **09/705,625**
Filed: **November 3, 2000**
For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

Sir:

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.
[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	* Minus** =		x0	$ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus*** =		x0	$ 40	$		x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					$		+ $270	$
				TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[X] Petition for extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Version With Markings to Show Changes Made and Terminal Disclaimer to Obviate a Provisional Double Patenting Rejection over a Pending Second Application**

[X] Check(s) in the amount of **$1030.00** is/are attached to cover:
[ ] 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: Terminal Disclaimer Fee

[X] The Assistant 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 the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on July 1, 2002.

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

300.1012 #7A m.m. 8/2/02

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Chih-Ming Chen, et al.
	Serial No.:	09/705,625
	Filed:	November 3, 2000
	For:	**Methods For Treating Diabetes Via Administartion Of Controlled Release Metformin**
	Examiner: T. Ware	Art Unit: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

July 1, 2002

AMENDMENT UNDER 37 C.F.R. §1.111

S i r:

In response to the Office Action dated December 31, 2001, please enter the following amendments and remarks:

IN THE CLAIMS

Please amend the claims as follows:

1. A method for 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 at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the agent at from 5.5 to 7.5 hours after administration.

2. The method of claim 1 wherein said at least one antihyperglycemic agent is a biguanide.

3. The method of claim 2 wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

22. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, based on administration of a 1700 mg once-a-day dose of metformin after an evening meal.

23. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

24. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

25. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

26. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $T_{1/2}$ from 2.8 to 4.4.

REMARKS

The undersigned attorney gratefully acknowledges the courtesies extended by Examiner Spear and Examiner Ware during the personal interview conducted at the United States Patent and Trademark Office on March 21, 2002.

I. Status of the Claims

Claims 1-34 are pending. Claims 1-3 and 22-26 have been amended. Support for the amendments to claims 1-3 are found in the original specification as filed, e.g., at page 4, lines 12-15; Support for the amendment to claim 22 is found in the original specification as filed, e.g., at page 28, table 1; support for the amendment to claim 23 is found in the original specification as filed, e.g., at page 30, table 3; support for the amendment to claim 24 is found in the original specification as filed, e.g., at page 35, table 6; support for the amendment to claim 25 is found in the original specification as filed, e.g., at page 32, table 5; support for the amendment to claim 26 is found in the original specification as filed, e.g., at page 28, table 1. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Information Disclosure Statement

In the Office Action, it was indicated that the Information Disclosure Statement filed on September 19, 2001 did not comply with 37 C.F.R. 1.98(a)(2). As discussed during the interview, it appears that the cited references became disassociated with the file and copies of the references cited in the Information Disclosure Statement will be resubmitted by hand delivery.

III. Rejections Under 35 U.S.C. § 112

In the Office Action, claims 4-31 were rejected as being indefinite on the grounds that "claims 4-31 require the method of claim 3, however claim 3 is a composition claims." In response, claim 3 has been amended to properly recite a method.

In the Office Action, claims 22-26 were rejected as being indefinite on the grounds that the claims are "omnibus type claims." In response, claims 21-25 have been amended as not to make reference to the Figures of the application.

In view of the actions taken, it is respectfully requested that the rejections under 35 U.S.C. § 112 be withdrawn.

IV. Rejections Under 35 U.S.C. § 102 and 35 U.S.C. § 103

In the Office Action, claims 1-15 and 19-34 were rejected as being anticipated and obvious over WO 00/28989 ("Lewis et al."), on the grounds that Lewis et al. "discloses controlled release metformin compositions [and] does not explicitly disclose the functional limitations of the instant claims, however since the formulations of [Lewis et al.] are substantially the same, it appears that the instant claimed functional limitations are inherent within [Lewis et al.]"

Claims 1-15 and 19-34 were rejected as being anticipated and obvious over U.S. Patent No. 5,955,106 ("Moeckel et al."), stating that Moeckel et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections".

Claims 1-15 and 19-34 were rejected as being anticipated and obvious over WO 99/47125 ("Cheng et al."), on the grounds that Cheng et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections ... [and Cheng et al.] discloses a semi-permeable membrane coating surrounding the core."

Claims 16-18 were rejected on the grounds of obviousness over the Lewis reference, the Moeckel reference or the Cheng reference, in view of Drug Facts and Comparisons (1999) which "is relied upon for teaching delivery of metformin in the presence or absence of food."

With respect to rejections under the doctrine of inherency, it is noted that as set forth in the MPEP, 8th edition, section 2122, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "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 recognized by one of ordinary skill. 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.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

It is further set forth in the MPEP, 8th edition, section 2122 that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to

reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. And Inter. 1990) (emphasis in original).

Further, as discussed during the interview, the Federal Circuit stated the following in *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 U.S.P.Q.2d 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. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.*

In view of the above discussion on the doctrine of inherency, the references cited by the Examiner are discussed below:

THE CHENG REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over WO 99/47125 ("Cheng et al.") is respectfully traversed as the Cheng reference has not been fully considered in its entirety.

As stated at page 3, lines 14-17 and at page 4, lines 6-9 of the Cheng reference, the formulations disclosed therein provide a controlled or sustained release formulation for an antihyperglycemic drug that obtain peak plasma levels approximately 8-12 hours after administration. Therefore, the administration of formulations which provide a T_{max} of the agent at from 5.5 to 7.5 hours after administration as recited in the present claims cannot be inherent by the administration of formulations disclosed in the Cheng reference. Further, the Cheng reference does not provide motivation to one skilled in the art to modify the formulations therein to obtain a T_{max} of the agent other than that which is specifically taught in the reference, i.e., a T_{max} of 8 to 12 hours.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Cheng reference.

THE LEWIS REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over WO 00/28989 ("Lewis et al.") is respectfully traversed.

As set forth in the MPEP, 8th edition, section 2112.02, under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior ar6t device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it cab be assumed that the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 19867).

The exemplified formulations of the Lewis reference are Examples 1-7 on pages 10-12. Example 1 describes a single or bilayer tablet comprising 4 or 8 mg of Compound I (an insulin sensitizer) and 1000 to 1500 mg of metformin HCl coated with an enteric coating of Eudragit L30 D-55, triethyl citrate and talc Alphafil 500 in the described percentages; Example 2 describes the single or bilayer tablets of Example 1 coated with a semi-permeable membrane of Eudragit RS30D, triethyl citrate and talc in the described percentages; Example 3 describes a non-disintegrating matrix single layer tablet of Compound I, metformin HCl and the described excipients in the described amounts, and a bilayer tablet to provide sustained release of Compound I and immediate release of metformin HCl with the described excipients in the described amounts; Example 4 describes a single and trilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 5 describes a single layer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 6 describes a single and bilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; and Example 7 describes a capsule containing multiple pellet cores having Compound I, metformin HCl with the described excipient in the described amounts.

The examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing a mean T_{max} from 5.5 to 7.5 hours after administration. Given the benefit of the information provided by the present specification, one skilled in the art would be able to modify other controlled release technologies in order to achieve these pharmacokinetic parameters.

As demonstrated above, the examples of the present application and the examples of the Lewis reference are directed to different controlled release technologies by virtue of their different ingredients, structure and methods of manufacture and it cannot be assumed that the prior art formulation would inherently perform the claimed method. Accordingly, a *prima facie* case of anticipation or obviousness based on inherency has not been established in the Office Action as there has not been provided a basis in fact and/or technical reasoning to reasonably support the determination that the prior art formulation would necessarily perform the method claimed.

Further, the Office Action has not taken into account the fact that there is no teaching in the Lewis reference to administer a formulation to arrive at the claimed T_{max} as recited in the present claims, nor does Lewis provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Lewis is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to administer a formulation to achieve a T_{max} from an antihyperglycemic agent controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). It is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Lewis reference.

THE MOECKEL REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over U.S. Patent No. 5,955,106 ("Moeckel et al.") is respectfully traversed.

At the very least, the Moeckel reference does not teach or suggest administration of the formulations described therein on a once-a-day basis as recited in the present claims.

Further, the same arguments set forth above with respect to the Lewis reference are applicable to the Moeckel reference.

The exemplified formulations of the Moeckel reference are Examples 1-7 on columns 5-9 of the patent. Example 1 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose,

Macrogol and titanium dioxide in the specified amounts; Example 2 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxyethylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropyl-cellulose, lactose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 3 describes a process of preparing a formulation with a core of metformin hydrochloride, sodium carboxy methyl cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 4 describes a process of preparing a formulation with a core of metformin hydrochloride, polyacrylic acid, methylhydroxypropylcellulose, and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 5 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxypropyl-cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of poly(ethylacrylate-methylacrylate, talcum and anti-foaming agent in the specified amounts; Example 6 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; and Example 7 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts.

As set forth above, the Examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing the claimed pharmacokinetic parameter of a mean T_{max} from 5.5 to 7.5 hours after administration.

Accordingly, the examples of the present application and the examples of the Moeckel reference are directed to different controlled release technologies by virtue of their different ingredients, structure and methods of manufacture. Accordingly, a *prima facie* case of anticipation or obviousness based on inherency has not been established as the Office Action has not provided a basis in fact and/or technical reasoning to reasonably support the determination

that the prior art formulation would necessarily perform the method claimed.

Further, the Office Action has not taken into account the fact that there is no teaching in the Moeckel reference to arrive at the claimed T_{max} as recited in the present claims, nor does Moeckel provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Moeckel is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to achieve a T_{max} from a biguanide controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). As stated above with respect to the Lewis reference, it is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Moeckel reference.

DRUG FACTS AND COMPARISONS

The rejection of claims 16-18 on the grounds of obviousness over the Lewis reference, the Moeckel reference or the Cheng reference, in view of Drug Facts and Comparisons (1999) is respectfully traversed.

This rejection is respectfully traversed as this reference fails to cure the deficiencies of the Lewis reference, the Moeckel reference and the Cheng reference as presented above. Namely, Drug Facts and Comparisons does not provide motivation to achieve a method of administering an antihyperglycemic formulation to provide a mean T_{max} from 5.5 to 7.5 hours of the agent after administration

V. Double Patenting Rejections

Claims 1-34 were provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-42 of copending application serial number no. 09/705,630.

In response, in order to expedite the issuance of a patent, a terminal disclaimer is submitted herewith over this copending application. Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental*

Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

Claims 1-34 were rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-29 of U.S. Patent no. 6,099,859; claims 1-39 of U.S. Patent No. 6,284,275; claims 1-4 of U.S. Patent No. 6,099,862. In the Office action, it was stated with respect to each reference that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in [the reference]." Further, claims 1-34 were provisionally rejected under obviousness type double patenting as being unpatentable over claims 1-54 of copending application no. 09/594,637 and over claims 1-29 of copending application no. 09/726,193 on the grounds that "the method claims disclose the compositions".

These rejections are respectfully traversed. It is submitted that the claimed pharmacokinetic parameter of a mean T_{max} of 5.5 to 7.5 hours after administration as recited in the present claims are not obvious in view of the claims of the cited references. As discussed during the interview, although formulations encompassed by the claims of these references may provide a T_{max} of between 5.5 to 7.5, the claimed pharmacokinetic parameters do not necessarily flow from formulations encompassed by these claims. Therefore, the Examiner is requested to remove these rejections.

VI. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

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.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

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

Davidson, Davidson & Kappel, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Version With Markings To Show Changes Made

IN THE CLAIMS

The following claim has been amended as follows:

1. (Amended) A method for 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 at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of [metformin] the agent at from 5.5 to 7.5 hours after administration.

2. (Amended) The [controlled release dosage form] method of claim 1 wherein said at least one antihyperglycemic agent is a biguanide.

3. (Amended) The [controlled release dosage form] method of claim 2 wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

22. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml [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 after an evening meal.

23. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml [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 after an evening meal.

24. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml [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 after an evening meal [at dinner].

25. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14^{th} day of administration [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 after an evening meal [at breakfast].

26. (Amended) The method of claim 22 [3], in which the administration of the at least one metformin dosage form provides a mean $T_{1/2}$ from 2.8 to 4.4 [about 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].

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING SECOND APPLICATION

Docket No. 300.1012

In re Application of: **Chih-Ming CHEN, et al.**

Application No. **09/705,625**

Filed: **November 3, 2000**

For: **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

The owner, **Andrx Corporation** of **100.00** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent g granted on pending second Application Number **09/705,630**, filed on **November 3, 2000**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

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 statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

3. Owner/applicant is ☐ Small entity ☒ Large entity

The terminal disclaimer fee under 37 CFR 1.20(d) is **$110.00** and is to be paid as follows:

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

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **50-0552**. A duplicate copy of this sheet is enclosed.

PTO suggested wording for terminal disclaimer was

☒ unchanged. ☐ changed (if changed, an explanation should be supplied.)

R. J. Paradiso

Signature

Dated: July 1, 2002

Name and Address of Person Signing

Robert J. Paradiso, Reg. No. 41,240
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
212-736-1940

07/12/2002 AOSHAN1 00000061 09705625
02 FC:148 110.00 OP

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) (Large Entity)	Docket No. 300.1012

In Re Application Of: Chih-Ming CHEN, et al.

Serial No.	Filing Date	Examiner	Group Art Unit
09/705,625	November 3, 2000	T. Ware	1615

Invention: METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a response to the Office Action of December 31, 2001 (Date) above-identified application.

The requested extension is as follows (check time period desired):

☐ One month ☐ Two months ☒ Three months ☐ Four months ☐ Five months

from: March 31, 2002 (Date) until: June 30, 2002 (Date)

The fee for the extension of time is $920 and is to be paid as follows:

COPY OF PAPERS ORIGINALLY FILED

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

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No.
A duplicate copy of this sheet is enclosed.

☒ If an additional extension of time is required, please consider this a petition therefor and charge any additional fees which may be required to Deposit Account No.
A duplicate copy of this sheet is enclosed.

Signature

Dated: July 1, 2002

Robert J. Paradiso, Reg. No. 41,240
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th floor
New York, New York 10018
212-736-1940

07/12/2002 AOSMAN1 00000061 09705625
01 FC:117 920.00 OP

cc:

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012	6705

23280 7590 12/31/2001

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

EXAMINER	
WARE, TODD	
ART UNIT	**PAPER NUMBER**
1615	4

DATE MAILED: 12/31/2001

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

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/705,625	Applicant(s) CHENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	

-- Th MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2001* .

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

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

Disposition of Claims

4)☒ Claim(s) *1-34* 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) *1-34* is/are rejected.

7)☒ Claim(s) *2 and 3* 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ 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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of declaration and fee filed 4-5-01 is acknowledged. Claims 1-34 are pending.

Claim Objections

1. Claims 2 and 3 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim: Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires a Tmax for metformin at 5.5 to 7.5 hours. Claim 2 broadens the scope of claim 1 to the class biguanides and claim 3 requires the active agent to be metformin, however, claim 1 already requires metformin.

Claim Rejections - 35 USC § 112

2. 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.

3. Claims 4-31 are 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.

Claims 4-31 require the method of claim 3, however claim 3 is a composition claim.

4. Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that they fail to point out what is included or excluded by the claim language. These claims are omnibus type claims.

Claim Rejections - 35 USC § 102

5. 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.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (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) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-15, 19-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Lewis et al (WO 00/28989; hereafter '989).

'989 discloses controlled release metformin compositions. '989 does not explicitly disclose the functional limitations of the instant claims, however since the formulations of '989 are substantially the same, it appears that the instant claimed functional limitations are inherent within '989. Therefore, the burden is shifted to applicants to demonstrate a difference between '989 and the instant claims (*In re Swinehart*, 169 USPQ 226 and *In re Fitzgerald* 205 USPQ 594).

7. Claims 1-15, 19-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125; hereafter '125).

'125 discloses controlled release metformin compositions and is relied upon for the same reasons set forth in the previous 35 U.S.C. 102(a) rejections as being anticipated by Lewis et al (WO 00/28989; hereafter '989).

8. Claims 1-15, 19-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Moeckel et al (5,955,106; hereafter '106).

'106 discloses controlled release metformin compositions and is relied upon for the same reasons set forth in the previous 35 U.S.C. 102(a) rejections as being anticipated by Lewis et al (WO 00/28989; hereafter '989).

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. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) or Cheng et al (WO 99/47125; hereafter '125) or Moeckel et al (5,955,106; hereafter '106) each alone or each in combination with Drug Facts and Comparisons (1999).

'989, '125, and '106 all teach controlled release metformin compositions. 'They do not explicitly teach the functional limitations of the instant claims, however since the formulations of these references are substantially the same, it appears that the instant claimed functional limitations are inherent. Therefore, the burden is shifted to applicants to demonstrate a difference between the prior art and the instant claims (*In re Swinehart*, 169 USPQ 226 and *In re Fitzgerald* 205 USPQ 594). Varying amounts of ingredients, such as dose, or administration in two dosage forms would have been

obvious to one skilled in the art at the time of the invention to provide a greater or lesser drug effect or, in the case of administration in two dosage forms, to administer a large dose in smaller tablets. '989, '125, and '106 do not teach the limitations of claims 16-17.

Drug Facts and Comparisons (DFC) is relied upon for teaching delivery of meformin in the presence or absence of food.

Accordingly, it would have been obvious to one skilled in the art at the time of the invention to administer the compositions at dinner or at a fed state with the motivation of regulating sugar levels.

12. Claims 1-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (6,270,805; hereafter '805) alone or in combination with Drug Facts and Comparisons (1999).

'805 discloses controlled release metformin compositions. '805 does not explicitly disclose some of the functional limitations of the instant claims, however since the formulations of '805 are substantially the same, it appears that the instant claimed functional limitations are inherent within '106. Therefore, the burden is shifted to applicants to demonstrate a difference between '106 and the instant claims (*In re Swinehart*, 169 USPQ 226 and *In re Fitzgerald* 205 USPQ 594). Varying amounts of ingredients, such as dose would have been obvious to one skilled in the art at the time of the invention to provide a greater or lesser drug effect.

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. See *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) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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 1-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in '859.

15. Claims 1-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be

inherent in '275. Also, buformin is an adjacent homolog of metformin and therefore metformin is obvious over buformin.

16. Claims 1-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in '275.

17. Claims 1-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 09/705,630. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims disclose the compositions.

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

18. Claims 1-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/726,193. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the method claims disclose the compositions.

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

19. Claims 1-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-54 of copending Application No. 09/594,637. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims disclose the compositions.

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

Conclusion

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

tw
December 21, 2001

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice of References Cited	Application/Control No. 09/705,625	Applicant(s)/Patent Under Examination HENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,284,275	09-2001	Chen et al	424/473
	B	US-6,270,805	08-2001	Chen et al	424/497
	C	US-6,099,862	08-2000	Chen et al	424/473
	D	US-6,099,859	08-2000	Cheng et al	424/464
	E	US-5,955,106	09-1999	Moeckel et al	424/464
	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	WO 00/28989	05-2000	WIPO	Lewis et al	
	O	WO 99/47125	09-1999	WIPO	Cheng et al	
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Drug Facts and Comparisons Page 635-642 1999
	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.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20

A1

(11) International Publication Number: **WO 99/47125**

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/US99/06024

(22) International Filing Date: 19 March 1999 (19.03.99)

(30) Priority Data:
09/045,330 20 March 1998 (20.03.98) US

(71) Applicant: ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US).

(72) Inventors: CHENG, Xiu, Xiu; Apartment 506, 3150 W. Rolling Hills Circle, Davie, FL 33328 (US). CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). JAN, Steve; 512 N.W. 120th Drive, Coral Springs, FL 33071 (US). CHOU, Joseph; 5755 N.W. 54th Place, Coral Springs, FL 33067 (US).

(74) Agent: ENDRES, Martin, P.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

(57) Abstract

A controlled release antihyperglycemic tablet that does not contain an expanding polymer and comprising a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane.

Same as
6099859

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

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 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.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride has been limited to the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® product which is a commercially available product from Bristol-Myers Squibb Co. containing metformin HCl.

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 and a 25% lower AUC in plasma 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.

It is an object of the present invention to provide a controlled or sustained release formulation for 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 for 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 for an antihyperglycemic drug that can provide continuous and 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.

It is an additional object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels approximately 8-12 hours after administration.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

SUMMARY OF THE INVENTION

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 semipermeable membrane coating surrounding the core; and

(c) at least one passageway in the semipermeable membrane.

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 antihypoglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form will be administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and provide therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 1 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 2 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 2 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 3 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 3 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 4 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 1 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 5 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the

commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 6 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions.

FIG. 7 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after breakfast).

FIG. 8 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after dinner).

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.

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-bis(ß-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.

The core of the present invention which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption 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 semipermeable membrane, preferably a modified polymeric membrane to form the controlled release tablet of the invention. The semipermeable membrane is permeable to the passage of an external fluid such as water and biological fluids and is impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the semipermeable 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 semipermeable 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 semipermeable 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, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

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 semipermeable membrane to form paths in the

semipermeable membrane for the fluid to enter the core and dissolve the active ingredient.

The semipermeable membrane may also be formed with commonly known excipients such 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, weaken 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 Patents such as 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607.

Generally, the membrane coating around the core will comprise from about 1% to about 5% and preferably about 2% to about 3% based on the total weight of the core and coating.

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 semipermeable

membrane of the dosage form or it may be incorporated into the semipermeable membrane.

In a preferred embodiment the dosage form will have the following composition:

	Preferred	Most Preferred
CORE:		
drug	50-98%	75-95%
binder	0-40%	3-15%
absorption enhancer	0-20%	2-10%
COATING:		
semipermeable polymer	50-99%	75-95%
flux enhancer	0-40%	2-20%
plasticizer	0-25%	2-15%

The dosage forms prepared according to the present invention should 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:

	Preferred	Most Preferred
Time (hours)		
2	0-25%	0-15%
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.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I Core	
metformin HCl	90.54%
povidone[1], USP	4.38%
sodium tribasic phosphate	4.58%
magnesium stearate	0.5 %

[1]approximate molecular weight = 50,000; dynamic viscosity (10%w/v solution at 20°C) = 5.5-8.5 m Pa s.

(a) Granulation

The metformin HCl is delumped by passing it through a 40 mesh screen and collecting it in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying the binding solution of povidone and sodium tribasic phosphate 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 (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(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, 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 spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	
cellulose acetate (398-10)[2]	85%
triacetin	5%
PEG 400	10%

[2]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

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 clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	9	12
4	27	32
8	62	82
12	82	100

16	88	105
20	92	108

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 1.

Figure 4 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example. Also shown in Figure 4 is the in vivo metformin plasma profile of GLUCOPHAGE®, a commercially available pharmaceutical product containing the drug metformin HCl.

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I Core	
metformin HCl	88.555%
povidone[3], USP	6.368%
sodium lauryl sulfate	4.577%
magnesium stearate	0.5 %

[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-90F, 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 coated granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(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 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 spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	
cellulose acetate (398-10)[4]	85%
triacetin	5%
PEG 400	10%

[4]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

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 clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	12
4	29	27
8	55	52
12	72	71
16	81	83
20	87	91

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 2.

Figure 5 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example under fasting conditions. Figure 5 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fasting conditions.

Figure 6 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example

under fed conditions. Figure 6 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fed conditions.

Figures 5 and 6 clearly show that the dosage forms prepared in accordance with the present invention exhibit consistent bioavailability under both fed and fasting conditions while the GLUOPHAGE® product's bioavailability decreases in the presence of food.

EXAMPLE 3

A controlled release tablet containing 850 mg of metformin HCl and having the same formula as in Example 2 is prepared as described in Example 2 except that an additional hole was drilled on the plain side of the coated tablet. The additional hole had a diameter of approximately 1 mm.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	14
4	27	28
8	50	63
12	67	84
16	84	95
20	97	102

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 3.

Figure 7 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after breakfast. Figure 7 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after breakfast.

Figure 8 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after dinner. Figure 8 also

shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after dinner.

Table 1 is a summary of the bioavailability comparision data, test/reference ratio, shown in Figures 4-8 wherein the GLUCOPHAGE® product is the reference product in a two way crossover biostudy with n = 6.

TABLE 1

Formula	Figure	Study	AUC	Cmax	Tmax
Ex. 1	4	Fasting	0.202	0.12	2.15
Ex. 2	5	Fasting	0.369	0.214	1.73
Ex. 2	6	Fed (bkft)	0.628	0.305	1.94
Ex. 3	7	Fed (bkft)	0.797	0.528	1.82
Ex. 3	8	Fed (dinner)	0.850	0.751	2.00

bkft = breakfast

The results reported in Table 1 and Figures 4-8 show that dosage forms prepared in accordance with the present invention exhibit an increase in the bioavailability of the antihyperglycemic drug in the presence of food, especially when taken with or shortly after the evening meal.

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.

We claim:

1. A controlled release pharmaceutical tablet comprising:

(a) a core comprising:

(i) an antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer; and

(b) a semipermeable membrane coating covering said core; and

(c) at least one passageway in the semipermeable membrane.

2. A controlled release pharmaceutical tablet as defined in claim 1 wherein the antihyperglycemic drug is a biguanide.

3. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is metformin or a pharmaceutically acceptable salt thereof.

4. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is buformin or a pharmaceutically acceptable salt thereof.

5. A controlled release pharmaceutical tablet as defined in claim 1 wherein the binding agent is water soluble.

6. A controlled release pharmaceutical tablet as defined in claim 1 wherein the water soluble binding agent is polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, waxes or mixtures thereof.

7. A controlled release pharmaceutical tablet as defined in claim 6 wherein the water soluble binding agent is polyvinyl pyrrolidone.

8. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is selected from

the group consisting of fatty acids, surfactants, chelating agents, bile salts or mixtures thereof.

9. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a fatty acid selected from the group consisting of capric acid, oleic acid or their monoglycerides.

10. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a surfactant selected from the group consisting of sodium lauryl sulfate, sodium taurocholate and polysorbate 80.

11. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a chelating agent selected from the group consisting of citric acid, phytic acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(ß-aminoethyl ether)-N,N,N,N-tetraacetic acid.

12. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a bile salt.

13. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is sodium lauryl sulfate.

14. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane around the core is a water insoluble cellulose derivative.

15. A controlled release pharmaceutical tablet as defined in claim 14 wherein the water insoluble cellulose derivative in the membrane around the core is cellulose acetate.

16. A controlled release pharmaceutical tablet as defined in claim 1 wherein semipermeable membrane comprises a flux enhancer.

17. A controlled release pharmaceutical tablet as defined in claim 16 wherein the flux enhancer is sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers or mixtures thereof.

18. A controlled release pharmaceutical tablet as defined in claim 17 wherein the flux enhancer is polyethylene glycol with an average molecular weight between 380 and 420.

19. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane comprises a plasticizer.

20. A controlled release pharmaceutical tablet as defined in claim 19 wherein the plasticizer is triacetin.

21. A controlled release pharmaceutical tablet as defined in claim 1 wherein at least two passageways are formed in the semipermeable membrane.

22. A controlled release pharmaceutical tablet as defined in claim 1 wherein the peak plasma level is obtained 8-12 hours after administration.

23. A controlled release pharmaceutical tablet as defined in claim 1 further comprising an effective amount of the antihyperglycemic drug coated onto the semipermeable membrane or mixed into the semipermeable membrane to

provide an immediate release of an effective amount of the antihyperglycemic drug.

24. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:

50-98% of the drug;

0-40% of the binding agent; and

0-20% of the absorption enhancer; and the coating comprises:

50-99% of the polymer;

0-40% of the flux enhancer; and

0-25% of the plasticizer.

25. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:

75-95% of the drug;

3-15% of the binding agent; and

2-10% of the absorption enhancer; and the coating comprises:

75-95% of the polymer;

2-20% of the flux enhancer; and

2-15% of the plasticizer.

26. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile 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:

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 not less than 50% of the drug is released;

after 16 hours not less than 60% of the drug is released; and after 20 hours not less than 70% of the drug is released.

27. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile 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:
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 not less than 60% of the drug is released;
after 16 hours not less than 70% of the drug is released;
and after 20 hours not less than 80% of the drug is released.

28. A controlled release pharmaceutical tablet as defined in claim 1 that is administered with or shortly after the evening meal.

29. A controlled release antihyperglycemic tablet comprising:
(a) a core consisting essentially of:
(i) metformin or a pharmaceutically acceptable salt thereof;
(ii) a water soluble binding agent; and
(iii) an absorption enhancer; and
(b) a semipermeable membrane coating covering said core comprising:
(i) cellulose acetate;
(ii) a flux enhancer; and
(iii) a plasticizer; and
(c) at least one passageway in the semipermeable membrane.

30. A controlled release pharmaceutical tablet as defined in claim 29 wherein the peak plasma level is obtained 8-12 hours after administration.

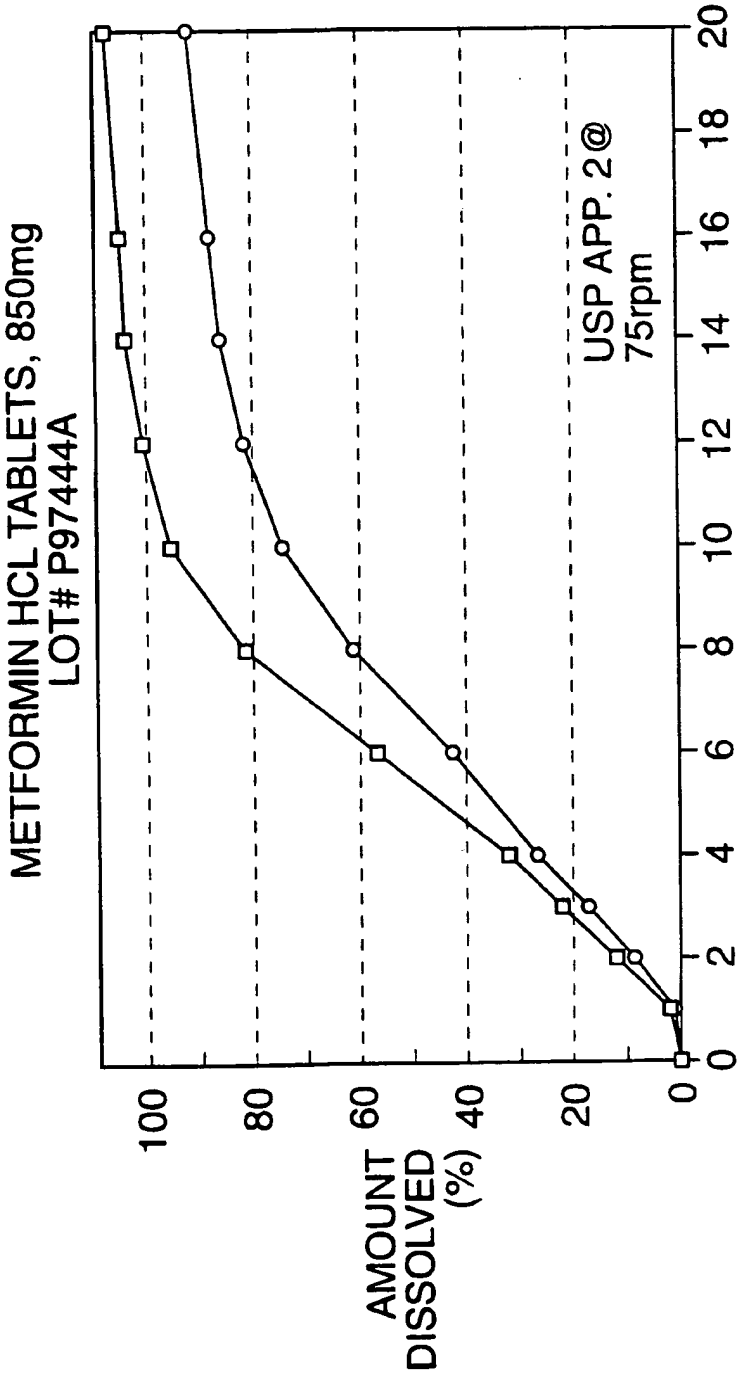


FIG. 1

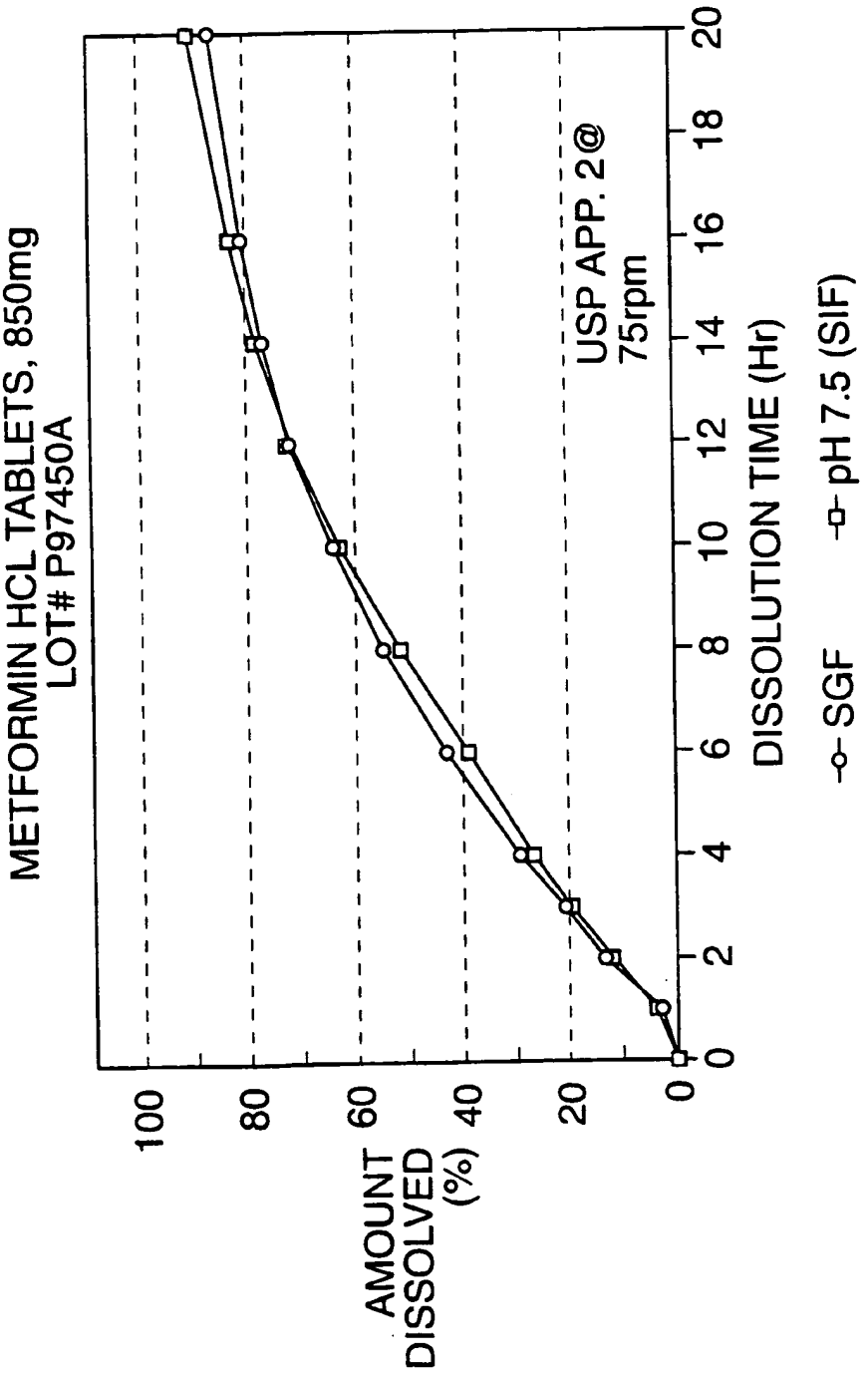


FIG. 2

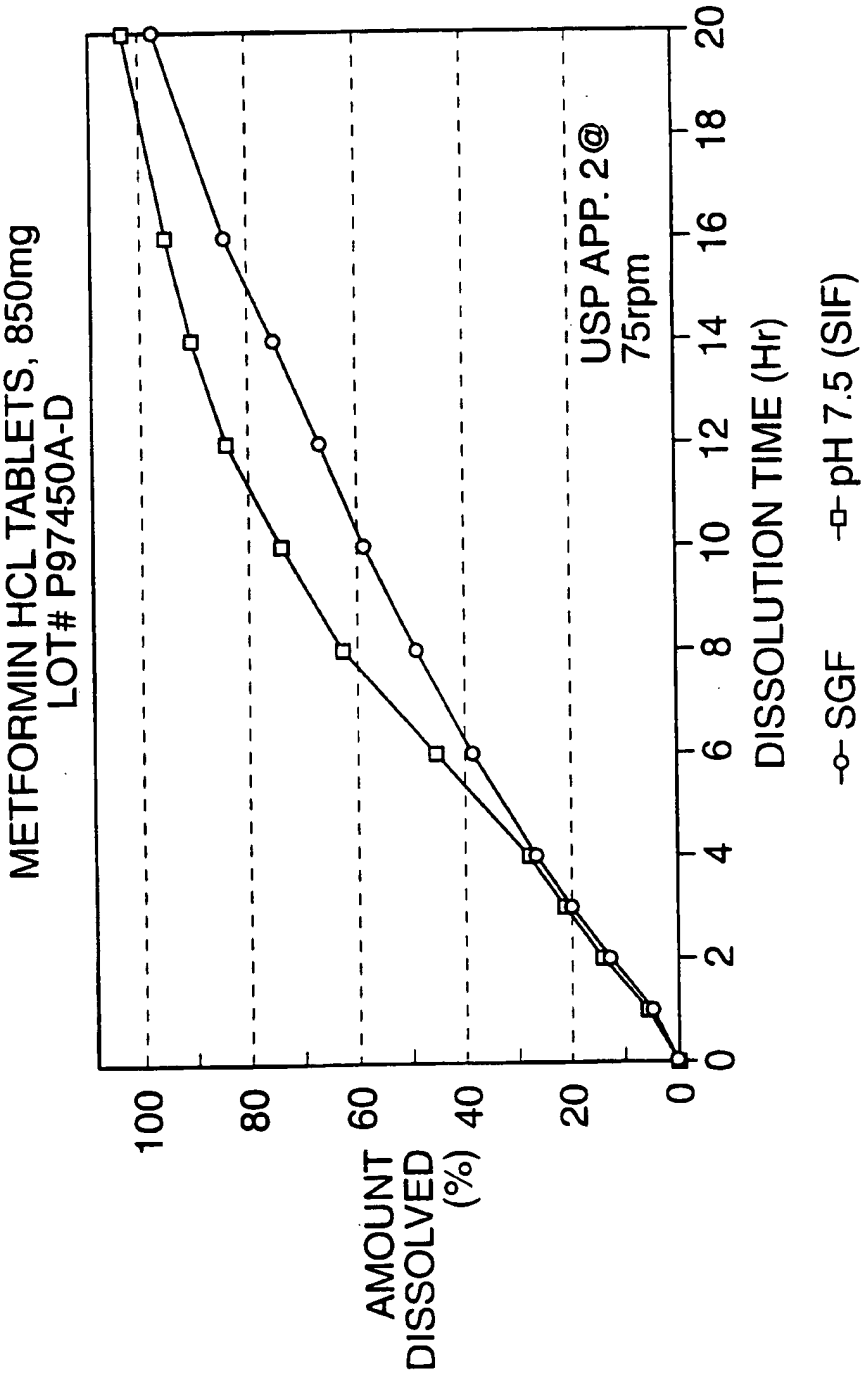


FIG. 3

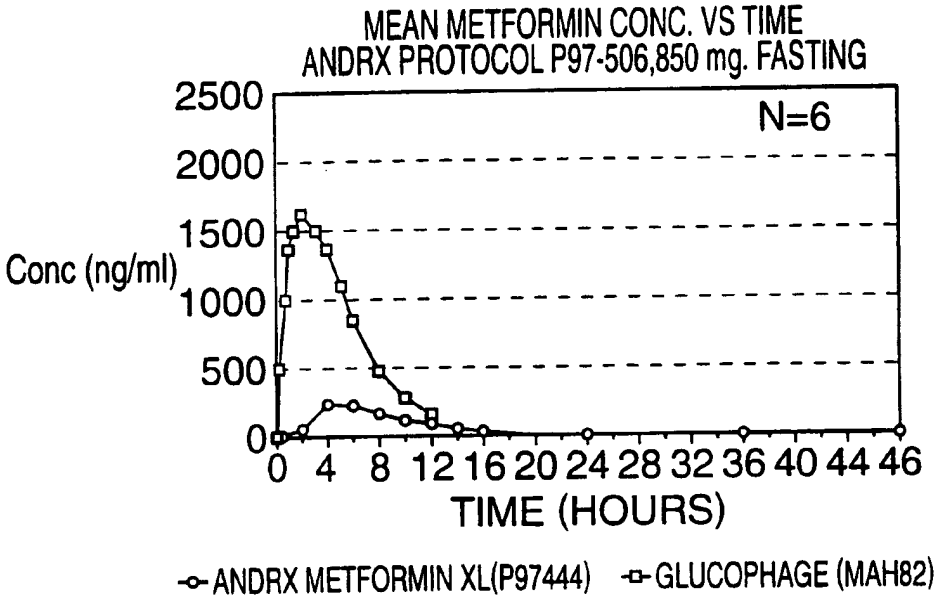

MEAN METFORMIN CONC. VS TIME
ANDRX PROTOCOL P97-506,850 mg. FASTING
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0 4 8 12 16 20 24 28 32 36 40 44 46
TIME (HOURS)
ANDRX METFORMIN XL(P97444)
GLUCOPHAGE (MAH82)

FIG. 4

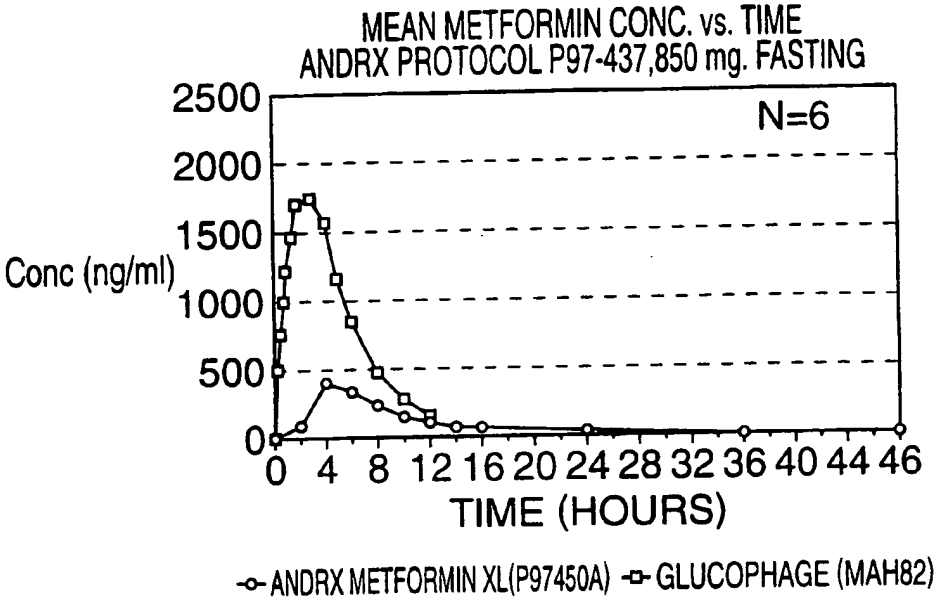


FIG. 5

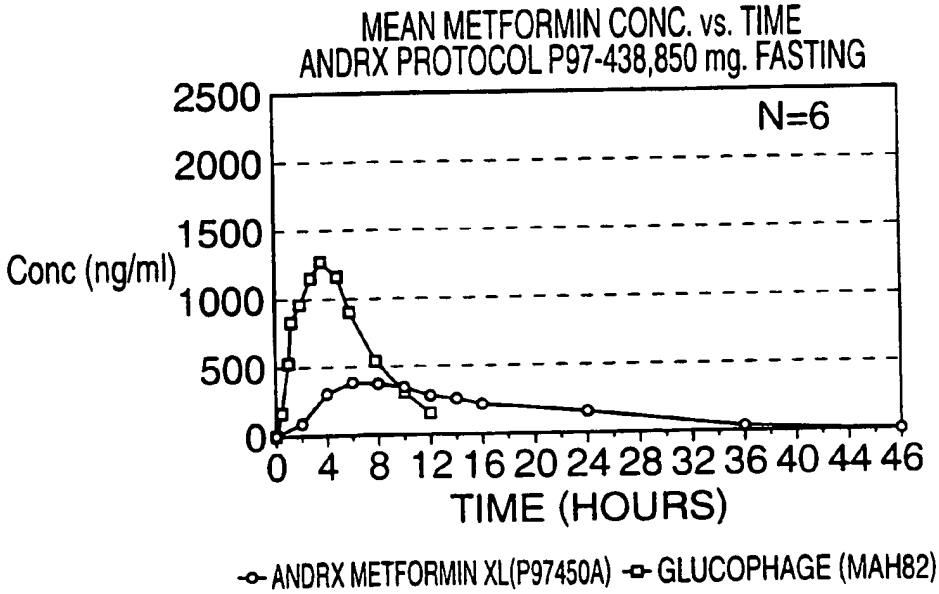


FIG. 6

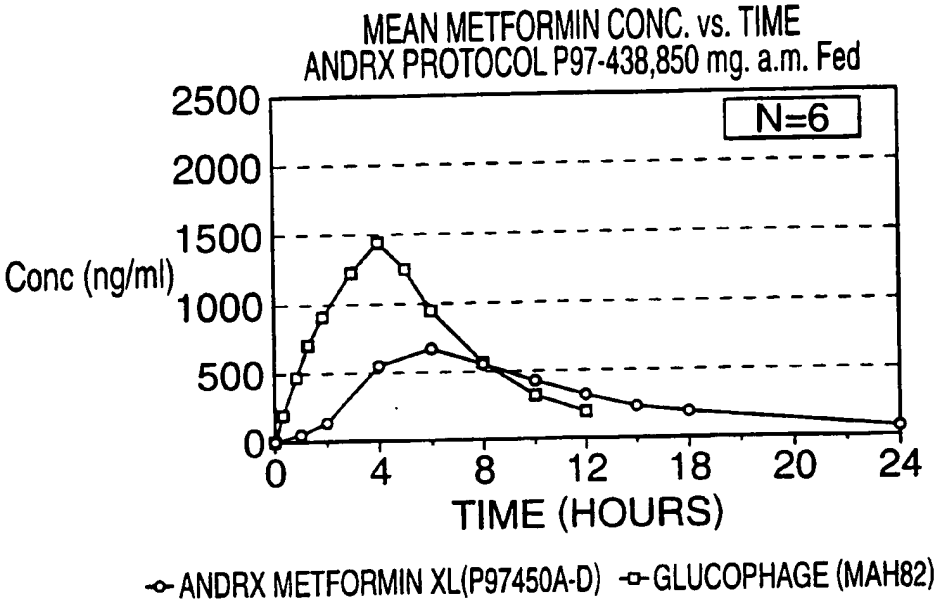

MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P97-438,850 mg. a.m. Fed
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
18
20
24
TIME (HOURS)
ANDRX METFORMIN XL(P97450A-D)
GLUCOPHAGE (MAH82)

FIG. 7

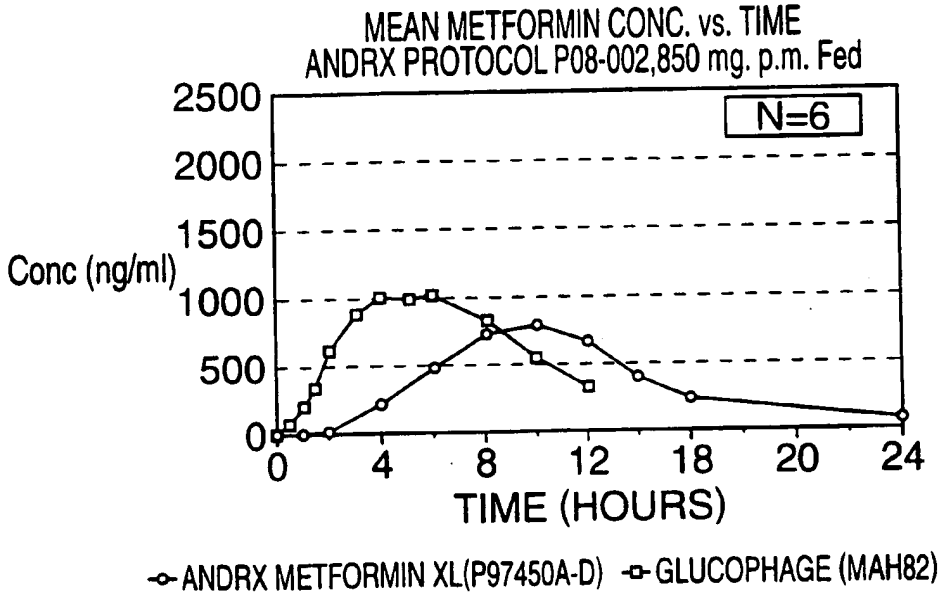

MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P08-002,850 mg. p.m. Fed
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
18
20
24
TIME (HOURS)
ANDRX METFORMIN XL(P97450A-D)
GLUCOPHAGE (MAH82)

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06024

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/20
US CL :424/464

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464

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

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

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,858,398 A (CHO) 12 JANUARY 1999, col. 1, lines 13-16; col. 3, lines 18-28; col. 11, lines 25-35; col. 12, lines 13-29, col. 15, lines 10,63; col. 16, lines 1-19; col. 18, lines 32-35; col. 19, lines 67; col. 20 lines 1-5.	1-30

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
21 APRIL 1999	24 JUN 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. Lawrence for THURMAN K. PAGE Telephone No. (703) 308-1235

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

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/353, 31/4439, 9/32, 9/52, 45/06, A61P 3/10

A1

(11) International Publication Number: **WO 00/28989**

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/EP99/08704

(22) International Filing Date: 8 November 1999 (08.11.99)

(30) Priority Data:

9824866.9	12 November 1998 (12.11.98)	GB
9824867.7	12 November 1998 (12.11.98)	GB
9824869.3	12 November 1998 (12.11.98)	GB
9912193.1	25 May 1999 (25.05.99)	GB
9912190.7	25 May 1999 (25.05.99)	GB
9912191.5	25 May 1999 (25.05.99)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LEWIS, Karen [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LILLIOTT, Nicola, Jayne [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). MACKENZIE, Donald, Colin [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). RE, Vincenzo [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: RUTTER, Keith; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE OF AN INSULIN SENSITISER AND ANOTHER ANTIDIABETIC AGENT

(57) Abstract

A pharmaceutical composition, which composition comprises: an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetes agent, and the use of such composition in medicine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE OF AN INSULIN SENSITISER AND ANOTHER ANTIDIABETIC AGENT

This invention relates to a novel composition, in particular to a modified release composition and its use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Alpha glucosidase inhibitor antihyperglycaemic agents (or alpha glucosidase inhibitors) and biguanide antihyperglycaemic agents (or biguanides) are commonly used in the treatment of Type 2 diabetes. Acarbose, voglibose, emiglitate and miglitol are examples of alpha glucosidase inhibitors. 1,1 - Dimethylbiguanidine (or metformin) is a particular example of a biguanide.

Insulin secretagogues are compounds that promote increased secretion of insulin by the pancreatic beta cells. The sulphonylureas are well known examples of insulin secretagogues. The sulphonylureas act as hypoglycaemic agents and are used in the treatment of Type 2 diabetes. Examples of sulphonylureas include glibenclamide (or glyburide), glipizide, gliclazide, glimepiride, tolazamide and tolbutamide.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as 'insulin sensitisers'. In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitisers.

Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of acyclic insulin sensitisers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now indicated that certain modified release pharmaceutical compositions allow administration of a single daily dose of Compound (I) and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, to provide an advantageous delivery of drug for maintaining effective glycaemic control with no observed adverse side effects. Such modified release is therefore considered to be particularly useful for the delivery of insulin sensitisers in combination with other antidiabetic agents for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

In another aspect, the invention provides a modified release pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent

Suitably, the release of both the insulin sensitiser and the other antidiabetic agent is modified.

However, it is envisaged that the release of only the insulin sensitiser is modified. It is also envisaged that the release of only the other antidiabetic agent is modified. The remaining active agent would of course be subject to non-modified release.

Suitably, the modified release is delayed, pulsed or sustained release.

In one aspect the modified release is a delayed release.

Delayed release is conveniently obtained by use of a gastric resistant formulation such as an enteric formulation, such as a tablet coated with a gastric resistant polymer, for example Eudragit L100-55. Other gastric resistant polymers include methacrylates, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phtahlate, in particular, Aquateric, Sureteric, HPMCP-HP-55S.

The enteric coated tablet may be a single layer tablet, where the active agents are admixed prior to compression into tablet form, or a multi-layer tablet, such as a bi-or tri-layer tablet, wherein each active agent is present in a discrete layer within the compressed

tablet form. The discrete table layers can be arranged as required to provide modified or non-modified release of each active agent.

In a further aspect 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.

Sustained release is typically provided by use of a sustained release matrix, usually in tablet form, such as disintegrating, non-disintegrating or eroding matrices.

Sustained release is suitably obtained by use of a non disintegrating matrix tablet formulation, for example by incorporating Eudragit RS into the tablet. Alternative non disintegrating matrix tablet formulations are provided by incorporating methacrylates, cellulose acetates, hydroxypropyl methylcellulose phtahlate, in particular Eudragit L and RL , Carbopol 971P, HPMCP-HP-55S into the tablet.

Sustained release is further obtained by use of a disintegrating matrix tablet formulation, for example by incorporating methacrylates, methylcellulose, in particular Eudragit L, Methocel K4M into the tablet.

Sustained release can also be achieved by using a semi-permeable membrane coated tablet for example by applying methacrylates, ethylcellulose, cellulose acetate, in particular Eudragit RS, Surelease to the tablet.

Sustained release can also be achieved by using a multi layer tablet, where each active ingredient is formulated together or as a separate layer, for example as a matrix tablet, with the other layers providing further control for sustained release of either one or both active agents.

In yet a further aspect the modified release is a pulsed release, for example providing up to 4, for example 2, pulses of active agent per 24 hours.

One form of pulsed release is a combination of non-modified release of active agent and delayed release.

Suitable modified release includes controlled release. The composition of the invention also envisages a combination of pulsed, delayed and/or sustained release for each of the active agents, thereby enabling for example the release of the reagents at different times. For example, where the composition comprises an insulin sensitiser and a biguanide, such as metformin, the composition can be arranged to release the metformin overnight.

A suitable alpha glucosidase inhibitor is acarbose.

Other suitable alpha glucosidase inhibitors are emiglitate and miglitol. A further suitable alpha glucosidase inhibitor is voglibose.

Suitable biguanides include metformin, buformin or phenformin, especially metformin.

Suitable insulin secretagogues include sulphonylureas.

Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, glimepiride, tolazamide and tolbutamide. Further sulphonylureas include acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide. Also included is the sulphonylurea glipentide.

Further suitable insulin secretagogues include repaglinide. An additional insulin secretagogue is nateglinide.

A preferred thiazolidinedione insulin sensitiser is Compound (I).

Other suitable thiazolidinedione insulin sensitisers include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone).

A particular thiazolidinedione insulin sensitiser is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

A particular thiazolidinedione insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone).

Suitable dosages, preferably unit dosages, of the insulin sensitiser and the other antidiabetic agent, such as the alpha glucosidase inhibitor, a biguanide or insulin secretagogue, include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

The dosages of each particular active agent in any given composition can as required vary within a range of doses known to be required in respect of accepted dosage regimens for that compound. Dosages of each active agent can also be adapted as required to take into account advantageous effects of combining the agents as mentioned herein.

In one particular aspect, the composition comprises 2 to 12 mg of Compound (I).

Suitably the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4mg of Compound (I).

Particularly, the composition comprises 4 to 8mg of Compound (I).

Particularly, the composition comprises 8 to 12 mg of Compound (I).

Preferably, the composition comprises 2 mg of Compound (I).

Preferably, the composition comprises 4 mg of Compound (I).

Preferably, the composition comprises 8 mg of Compound (I).

Suitable unit dosages of other insulin sensitisers include from 100 to 800mg of troglitazone such as 200, 400, 600 or 800mg or from 5 to 50mg, including 10 to 40mg, of pioglitazone, such as 20, 30 or 40 mg and also including 15, 30 and 45mg of pioglitazone.

As indicated above the unit doses of the additional antidiabetic agents including the alpha glucosidase inhibitor, the biguanide and the insulin secretagogue include those found in the reference texts mentioned herein and include the doses set out below.

For the alpha glucosidase inhibitor, a suitable amount of acarbose is in the range of from 25 to 600 mg, including 50 to 600 mg, for example 100mg or 200mg.

For the the biguanide, a suitable dosage of metformin is between 100 to 3000mg, for example 250, 500mg, 850mg or 1000mg.

For the insulin secretagogue, a suitable amount of glibenclamide is in the range of from 2.5 to 20 mg, for example 10mg or 20mg; a suitable amount of glipizide is in the range of from 2.5 to 40 mg; a suitable amount of gliclazide is in the range of from 40 to 320 mg; a suitable amount of tolazamide is in the range of from 100 to 1000 mg; a suitable amount of tolbutamide is in the range of from 1000 to 3000 mg; a suitable amount of chlorpropamide is in the range of from 100 to 500 mg; and a suitable amount of gliquidone is in the range of from 15 to 180 mg. Also a suitable amount of glimepiride is 1 to 6mg and a suitable amount of glipentide is 2.5 to 20mg.

A suitable amount of repaglinide is in the range of from 0.5mg to 20mg, for example 16mg. Also a suitable amount of nateglinide is 90 to 360mg, for example 270mg.

The compounds mentioned herein, in particular the thiazolidinediones such as Compound (I), may exist in one of several tautomeric forms, all of which are encompassed by the invention as individual tautomeric forms or as mixtures thereof. The compounds mentioned herein may contain one or more chiral carbon atoms and hence can exist in two or more stereoisomeric forms, all of which are encompassed by the invention either as individual isomers or as mixtures of isomers, including racemates.

It will be understood that the insulin sensitiser, such as Compound (I) and the other antidiabetic agent are in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate to the relevant pharmaceutically active agent chosen. In certain instances herein the names used for the antidiabetic agent may relate to a particular pharmaceutical form of the relevant active agent: It will be understood that all

pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable forms of the insulin sensitiser and other antidiabetic agent depend upon the particular agent used but included are known pharmaceutically acceptable forms of the particular agent chosen. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above mentioned publications. For example, a particular form of metformin is metformin hydrochloride, a particular form of repaglinide is a benzoic acid salt form and a particular form of tolbutamide is a sodium salt form.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0306228 and WO94/05659, especially pharmaceutically acceptable salted or solvated forms. A preferred pharmaceutically acceptable salt form of Compound (I) is a maleate. A preferred pharmaceutically acceptable solvated form of Compound (I) is a hydrate. A preferred form of pioglitazone is as the hydrochloride salt.

The insulin sensitiser or the alpha glucosidase inhibitor antihyperglycaemic agent of choice is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions

associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

For the avoidance of doubt, unless other wise stated, when reference is made herein to scalar amounts, including mg amounts, of the active compound such as Compound (I), in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of the active compound *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which provides 2 mg of Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., 'Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements', Clinical Products 1988.

In a preferred aspect, the dosage level of each of the active agents when used in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

There is also an indication that the treatment of the invention will effect an improvement, relative to the non-modified release of the individual agents, in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

In a further aspect the invention also provides a process for preparing a pharmaceutical composition, suitably for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a

human, which composition comprises an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, which process comprises formulating the insulin sensitiser, the other antidiabetic agent and the pharmaceutically acceptable carrier so as to enable a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

In a further aspect, the invention provides a process for preparing a modified release pharmaceutical composition, suitably for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises an insulin sensitiser, such as Compound (I) and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue and a pharmaceutically acceptable carrier therefor, which process comprises formulating the insulin sensitiser, the other antidiabetic agent and the pharmaceutically acceptable carrier so as to enable a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

The compositions are formulated to provide the modified release of active agents according to the appropriate methods required, for example those disclosed in Sustained and Controlled Release Drug Delivery Systems, Editor Joe R Robinson, Volume 7, published by Marcel Dekker under the title Drugs and the Pharmaceutical Sciences, Controlled Drug Delivery, 2nd Edition' edited by Joe Robinson and Vince Lee, Marcel Dekker, 1987 and 'Drug Delivery to the Gastrointestinal Tract' Editors: J G Hardy, S S. Davis and C G Wilson also with reference to texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

Preferably, the compositions are in unit dosage form. Unit dosage presentation forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants and wetting agents.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, tragacanth.

Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible

sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, xylitol.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, talc.

Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrilin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate.

As required the solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

No adverse toxicological effects are expected for the compositions of the invention in the above mentioned dosage ranges.

EXAMPLES COMPRISING AN INSULIN SENSITISER AND A BIGUANIDE

Example 1, Delayed Release Composition

Delayed release is achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 500, preferably, or 1000 or 1500mg of metformin HCl with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2, Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or bilayer tablets each comprising 4mg or 8mg of Compound (I) and 500, preferably, or 1000 or 1500mg of metformin HCl

Example 3, Sustained Release by use of a non disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	1000

(b) a bilayer tablet to provide sustained release of Compound I and immediate (i.e non-modified) release of metformin HCl.

Layer A	mg/tablet
Compound (I)	4 (pfb)

Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Layer B	mg/tablet
Metformin HCl	500
Polyvinyl pyrollidone	15
Magnesium stearate to	520

Example 4, Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	2.6
Magnesium stearate	3.25
Lactose monohydrate to	650

(b) a trilayer tablet:

Layer A	mg/tablet
Compound (I)	4 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Metformin HCl	250
Eudragit L100-55	74
Eudragit RS powder to	345

Layer C	mg/tablet
Metformin HCl	250
Polyvinyl pyrrolidone	7.5
Magnesium stearate to	260

Example 5, Sustained Release by use of a disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	74
Methocel K4M	18.5
Colloidal Silicon dioxide	2.6
Magnesium stearate	3.25
Lactose monohydrate to	650

Example 6, Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as single or bilayer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	650

Example 7, Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	4 (pfb)
Metformin HCl	500
Microcrystalline cellulose to	650

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

EXAMPLES COMPRISING AN INSULIN SENSITISER AND AN INSULIN SECRETAGOGUE

Example 1, Delayed Release Composition

Delayed release can be achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 2.5, 10 or 20 mg of glibenclamide with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2, Sustained Release by use of a matrix tablet (single layer)

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
glibenclamide	10
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Example 3, Sustained Release and Non-modifie Release by use of a matrix tablet (bilayer)

A matrix tablet is formed by tabletting the following mixture as a bilayer tablet to provide sustained release of Compound I and immediate (i.e non-modified) release of glibenclamide :

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to:	500

Layer B	mg/tablet
Glibenclamide	10
Polyvinylpyrrolidone	12.5
Sodium starch glycolate	10

Lactose monhydrate to	250

Example 4, Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or multi layer tablet each comprising 4mg or 8mg Compound (I) (pfb) and 2.5, 10 (preferably) or 20mg Glibenclamide.

Example 5, Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Glibenclamide	10
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

(b) a bilayer tablet:

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Glibenclamide	10
Eudragit L100-55	74
Eudragit RS powder	18.5

Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Example 6, Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as single or bilayer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Glibenclamide	10
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	150

Example 7, Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	8 (pfb)
Glibenclamide	10
Microcrystalline cellulose	133.5
Lactose monohydrate to	267

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

EXAMPLES COMPRISING AN INSULIN SENSITISER AND AN ALPHA GLUCOSIDASE INHIBITOR.

Example 1, Delayed Release Composition

Delayed release can be achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 100mg acarbose with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2, Sustained Release by use of a matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	600

(b) a bilayer tablet to provide sustained release of Compound (I) and non modified (i.e immediate) release of acarbose :

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Layer B	mg/tablet
Acarbose	100
Microcrystalline cellulose	134
Starch	12.5
Colloidal silicon dioxide	1.25
Magnesium stearate to	250

Example 3, Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or multi layer tablets each comprising 4mg or 8mg Compound (I) (pfb) and 100mg Acarbose

Example 4, Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	1
Magnesium stearate	2.5
Lactose monohydrate to	250

(b) a bilayer tablet:

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Acarbose	100
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	250

Example 5, Sustained Release by use of a Disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	74
Methocel K4M	18.5

Colloidal Silicon dioxide	1
Magnesium stearate	2.5
Lactose monohydrate to	250

Example 6, Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single or bilayer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	250

Example 7, Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	8 (pfb)
Acarbose	100
Microcrystalline cellulose	133.5
Lactose monohydrate to	267

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

Claims:

1. A pharmaceutical composition, which composition comprises: an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

2. A modified release pharmaceutical composition, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetes agent.

3. A composition according to claim 1 or claim 2, wherein the release of both the insulin sensitiser and the other antidiabetes agent is modified.

4. A composition according to any one of claims 1 to 3, wherein the modified release is a delayed release.

5. A composition according to claim 4, wherein the composition is in the form of an enteric tablet formulation.

6. A composition according to claim 5, wherein the enteric coated tablet is a single layer tablet.

7. A composition according to claim 7, wherein the enteric coated tablet is a multi-layer tablet.

8. A composition according to any one of claims 5 to 7, wherein the tablet is coated with a gastric resistant polymer.

9. A composition according to claim 8, wherein the gastric resistant polymer is selected from the list consisting of Eudragit L100-55, methacrylates, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phtahlate, in particular, Aquateric, Sureteric and HPMCP-HP-55S.

10. A composition according to any one of claims 1 to 3, wherein the modified release is a sustained release.

11. A composition according to any one of claims 1 to 3, wherein the sustained release is provided by a sustained release matrix selected from disintegrating, non-disintegrating and eroding matrices.

13. A composition according to claim 11, wherein the non disintegrating matrix tablet formulation is provided by incorporating Eudragit RS, methacrylates, cellulose acetates, hydroxypropyl methylcellulose phthalate, Carbopol 971P or HPMCP-HP-55S into the matrix.

14. A composition according to claim 11, wherein the disintegrating matrix tablet formulation is provided by incorporating methacrylates, methylcellulose and Methocel K4M into the matrix.

15. A composition according to any one of claims 1 to 14, wherein the insulin sensitiser is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (pioglitazone) or (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (troglitazone); or a derivative thereof.

16. A composition according to any one of claims 1 to 15, wherein the alpha glucosidase inhibitor is acarbose, emiglitate, miglitol or voglibose.

17. A composition according to any one of claims 1 to 15, wherein the biguanide is metformin, buformin or phenformin.

18. A composition according to any one of claims 1 to 15, wherein the insulin secretagogues is a sulphonylurea selected from glibenclamide, glipizide, gliclazide, glimepiride, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide, glipentide.

19. A composition according to any one of claims 1 to 15, wherein the insulin secretagogue is repaglinide or nateglinide.

INTERNATIONAL SEARCH REPORT

I. ıational Application No
PCT/EP 99/08704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/353 A61K31/4439 A61K9/32 A61K9/52 A61K45/06 A61P3/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 861 666 A (TAKEDA CHEMICAL INDUSTRIES LTD) 2 September 1998 (1998-09-02) page 10, line 3 - line 31 page 11 -page 12; examples 1,2 page 8, line 39 - line 57 page 9, line 39 - line 55 claims 12,13,15,24,26 ---	1-6, 8-11, 15-18
X	WO 98 11884 A (KNOLL AG ;BAILEY CLIFFORD JAMES (GB); JACKSON HELEN CHRISTINE (GB)) 26 March 1998 (1998-03-26) page 4, line 20 -page 5, line 3 page 12, line 29 -page 13, line 7 claims 21-25 --- -/--	1-6, 8-11,15, 17,18

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	07/04/2000

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

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

INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/EP 99/08704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 42340 A (CIRD GALDERMA ;FANJOL ANDREA (US); PFAHL MAGNUS (US); LERNHARDT WA) 1 October 1998 (1998-10-01) abstract claims 1-15	1-6,10, 15
X	US 5 502 078 A (HOLLOWAY BRIAN R ET AL) 26 March 1996 (1996-03-26)	1-6,10, 11
Y	column 3, line 32 - line 53	13,14
Y	DE 44 32 757 A (BOEHRINGER MANNHEIM GMBH) 21 March 1996 (1996-03-21) page 3, line 41 -page 4, line 31 page 7 -page 8; example 4	13,14
P,X	WO 99 03477 A (BUCKINGHAM ROBIN EDWIN ;SMITH STEPHEN ALISTAIR (GB); SMITHKLINE BE) 28 January 1999 (1999-01-28) page 2, line 19 -page 3, line 2 page 6, line 13 -page 7, line 18 page 10 claims 1-22	1-6,15, 17-19

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

Inventor Information

Inventor One Given Name::	Chih-Ming
Family Name::	Chen
Postal Address Line One::	10680 SW 40th Manor
City::	Davie
State::	Florida
Country::	United States
Postal or Zip Code::	33328
Citizenship Country::	United States
Inventor Two Given Name::	Xiu-Xiu
Family Name::	Cheng
Postal Address Line One::	3150 W. Rolling Hills Circle #506
City::	Davie
State::	Florida
Country::	United States
Postal or Zip Code::	33328
Citizenship Country::	United States
Inventor Three Given Name::	Steve
Family Name::	Jan
Postal Address Line One::	512 NW 120 Drive
City::	Coral Springs
State::	Florida
Country::	United States
Postal or Zip Code::	33071
Citizenship Country::	United States
Inventor Four Given Name::	Joseph
Family Name::	Chou
Postal Address Line One::	6232 Treywood Lane
City::	Manassas
State::	Virginia
Country::	United States
Postal or Zip Code::	20112
Citizenship Country::	United States

Correspondence Information

Correspondence Customer Number::	23280
Telephone::	(212) 736-1940
Fax::	(212) 736-2427
Electronic Mail::	ddk@ddkpatent.com

Application Information

Title Line One::	Methods For Treating Diabetes Via
Title Line Two::	Administration Of Controlled Release
Title Line Three::	Metformin
Total Drawings Sheets::	8
Formal Drawings::	No
Application Type::	Utility
Docket Number::	300.1012

Representative Information

Representative Customer Number::	23280

Assignee Information

Name::	Andrx Corporation
Postal Address Line One::	4001 SW 47th Avenue
City::	Fort Lauderdale
State::	Florida
Country::	United States
Postal or Zip Code::	33314

Docket No.: 300.1012

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: METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN, the specification of which

___ is attached hereto
X was filed on November 3, 2000 as Application Serial No. 09/705,625 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	Full name of joint Inventor, if any Xiu Xiu Cheng
Inventor's signature [signature]	Second Inventor's signature [signature]
Date 3/14/01	Date 3/22/01
Residence (city) _____, (state or country) _____	Residence (city) _____, (state or country) _____
Citizenship UNITED STATES	Citizenship UNITED STATES
Post Office Address: _____	Post Office Address: _____

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 Joseph Chou

Date 3/1/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

UNITED STATES PATENT & TRADEMARK OFFICE

Re: Application of: Chih-Ming Chen, et al.

Serial No.: 09/705,625

Filed: November 3, 2000

For: **Methods for Treating Diabetes Via Administration Of Controlled Release Metformin**

BOX: MISSING PARTS
Assistant Commissioner for Patents
Washington, D.C. 20231

April 2, 2001

RESPONSE TO NOTICE TO FILE MISSING PARTS

S i r:

In response to the Notification of Missing Requirements dated February 2, 2001, a copy of which is enclosed, please find an executed Declaration/Power of Attorney form signed by the inventors, and a check in the amount of $1092.00 covering the basic filing fee, additional claims fee, and surcharge.

If any additional fees are deemed to be due at this time, the Assistant Commissioner is authorized to charge payment of the same to Deposit Account No. 50-0552.

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

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, DC 20231" on April 2, 2001 .
DAVIDSON, DAVIDSON & KAPPEL, LLC
BY:_____

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

FORMALITIES LETTER

OC000000005728378

Date Mailed: 02/02/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $252.
  - $**252** for **14** total claims over 20.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

- **The balance due by applicant is $ 1092.**

A copy of this notice MUST be returned with the reply.

710.00 OP
130.00 OP
252.00 OP

02/09/2001 AGDITOM 00000027 09705625
01 FC:101
02 FC:105
03 FC:103

L Monroe

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

MC

FORM PTO-1083

Docket No.: **300.1012**
Date: **April 2, 2001**

Sector
#

ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

In re application of: **Chih-Ming Chen, et al.**
Serial No.: **09/705,625**
Filed: **November 3, 2000**
For: **Methods For Treating Diabetes Via Administration Of Controlled Release Metformin**

S i r:

Transmitted herewith is a **Response to Notice to File Missing Parts** 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	FEE	OR	LARGE ENTITY RATE	FEE
TOTAL CLAIMS	*	Minus**		=	0	x $ 9	$		x $ 18	$
INDEP. CLAIMS	*	Minus***		=	0	x $ 40	$		x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM						+ $135	$		+ $270	$
						TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[ ] Petition for extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Copy of Notice to File Missing Parts of Nonprovisional Application**
Declaration and Power of Attorney
Application Data Sheet

[X] Check(s) in the amount of **$1092.00** is/are attached to cover:
[X] Filing fee for additional claims under 37 C.F.R. 1.16
[ ] Petition fee for extension under 37 C.F.R. 1.136
[X] Other: **Basic Filing Fee**
Late Filing Fee Surcharge

[X] The Assistant 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 the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on April 2, 2001.

DAVIDSON, DAVIDSON & KAPPEL, LLC
BY:

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/705,625	11/03/2000	Xiu Xiu Cheng	300.1012

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

FORMALITIES LETTER

OC000000005728378

Date Mailed: 02/02/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $252.
  - $**252** for **14** total claims over 20.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

- **The balance due by applicant is $ 1092.**

A copy of this notice MUST be returned with the reply.

B Monroe

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

Express Mail Label No. EL 415 728 697 US

11-06-00

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012

Total Pages in this Submission
55

11/03/00 U.S. PTO 09/705625

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

and invented by:

Xiu Xiu CHENG, Chih-Ming CHEN, Steve JAN and Joseph CHOU

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Enclosed are:

Application Elements

1. ☐ Filing fee as calculated and transmitted as described below

2. ☒ Specification having 42 pages and including the following:

   a. ☒ Descriptive Title of the Invention
   b. ☐ Cross References to Related Applications *(if applicable)*
   c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   d. ☐ Reference to Microfiche Appendix *(if applicable)*
   e. ☒ Background of the Invention
   f. ☒ Brief Summary of the Invention
   g. ☒ Brief Description of the Drawings *(if drawings filed)*
   h. ☒ Detailed Description
   i. ☒ Claim(s) as Classified Below
   j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   - a. ☐ Formal Number of Sheets _____
   - b. ☒ Informal Number of Sheets 8

4. ☐ Oath or Declaration
   - a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   - b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   - c. ☐ With Power of Attorney ☐ Without Power of Attorney
   - d. ☐ *DELETION OF INVENTOR(S)*
     Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche *(Appendix)*

7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
   - a. ☐ Paper Copy
   - b. ☐ Computer Readable Copy *(identical to computer copy)*
   - c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*

9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☒ Acknowledgment postcard

14. ☒ Certificate of Mailing
    - ☐ First Class ☒ Express Mail *(Specify Label No.):* EL 415 728 697 US

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

17. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	34	- 20 =	14	x	$18.00	$252.00
Indep. Claims	2	- 3 =	0	x	$80.00	$0.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$710.00
OTHER FEE *(specify purpose)* _____						$0.00
					TOTAL FILING FEE	$962.00

☐ A check in the amount of to cover the filing fee is enclosed.

☐ The Commissioner is hereby authorized to charge and credit Deposit Account No. as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☐ Credit any overpayment.
- ☐ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Signature

Robert J. Paradiso
Reg. No. 41,240

Dated: **November 3, 2000**

23280
PATENT TRADEMARK OFFICE

cc:

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

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

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

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:

(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

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_{0-24hr} 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_{0-24hr} from at least 80%, preferably at least 90% of the mean AUC_{0-24} 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

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

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

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.

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.

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.

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.

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

(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.

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

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.

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

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%

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

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.

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.

(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).

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.

(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).

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.

(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).

(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.

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:

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

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:

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) 357 (between doses)	882 882	1.8 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.

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

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).

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.

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	$AUC_{0\text{-}24hr}$ (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	T_{lag} (hr)	$t_{½}$ (hr)	$AUC_{0\text{-}24hr}$	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.

WHAT IS CLAIMED IS:

1. A method for 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 at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration.

2. The controlled release dosage form of claim 1 wherein said at least one antihyperglycemic agent 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 method of claim 3, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 5.5 to 7.0 hours after the administration.

6. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at breakfast and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 6.0 to about 7.5 hours after the administration.

7. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

8. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

9. The method of claim 3, in which the administration of the at east one metformin dosage form 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 administration.

10. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

11. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

12. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

13. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

14. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from 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.

15. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ that is from at least 90% 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.

16. The method of claim 3, in which the once-a-day dose of the metformin is administered at dinner.

17. The method of claim 16, in which the once-a-day dose of metformin is administered at fed state.

18. The method of claim 16, in which the once-a-day dose of the metformin is about 2000 mg, which is provided by two controlled release dosage forms containing about 1000 mg metformin each.

19. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

20. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

21. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

22. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

23. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

24. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

25. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set

forth in FIG. 6, based on administration of a 2000 mg once-a-day dose of metformin at breakfast.

26. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma glucose concentration-time profile substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

27. The method of claim 3, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. The method of claim 3, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. The method of claim 3, in which the dose of metformin comprises metformin hydrochloride.

30. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 1000 mg to about 2500 mg.

31. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 2000 mg to about 2500 mg metformin.

32. A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering 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 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.

33. The method of claim 32 wherein said dosage form maintains bioavailability from at least 80% of the immediate release composition.

34. The method of claim 32 wherein said dosage form maintains bioavailability from aat least 90% of the immediate release composition.

ABSTRACT

A method 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 a 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.

FIGURE 1

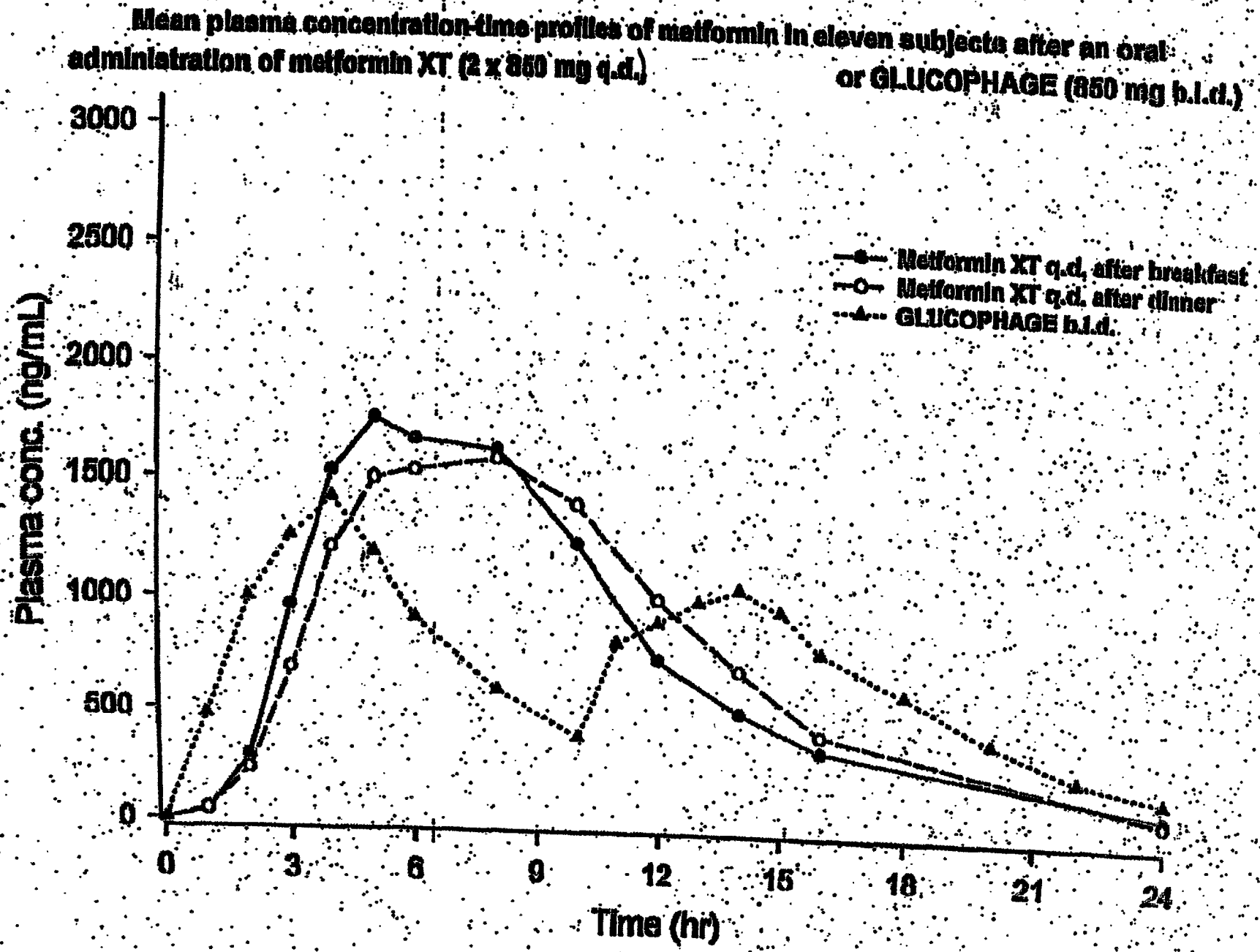


FIGURE 2

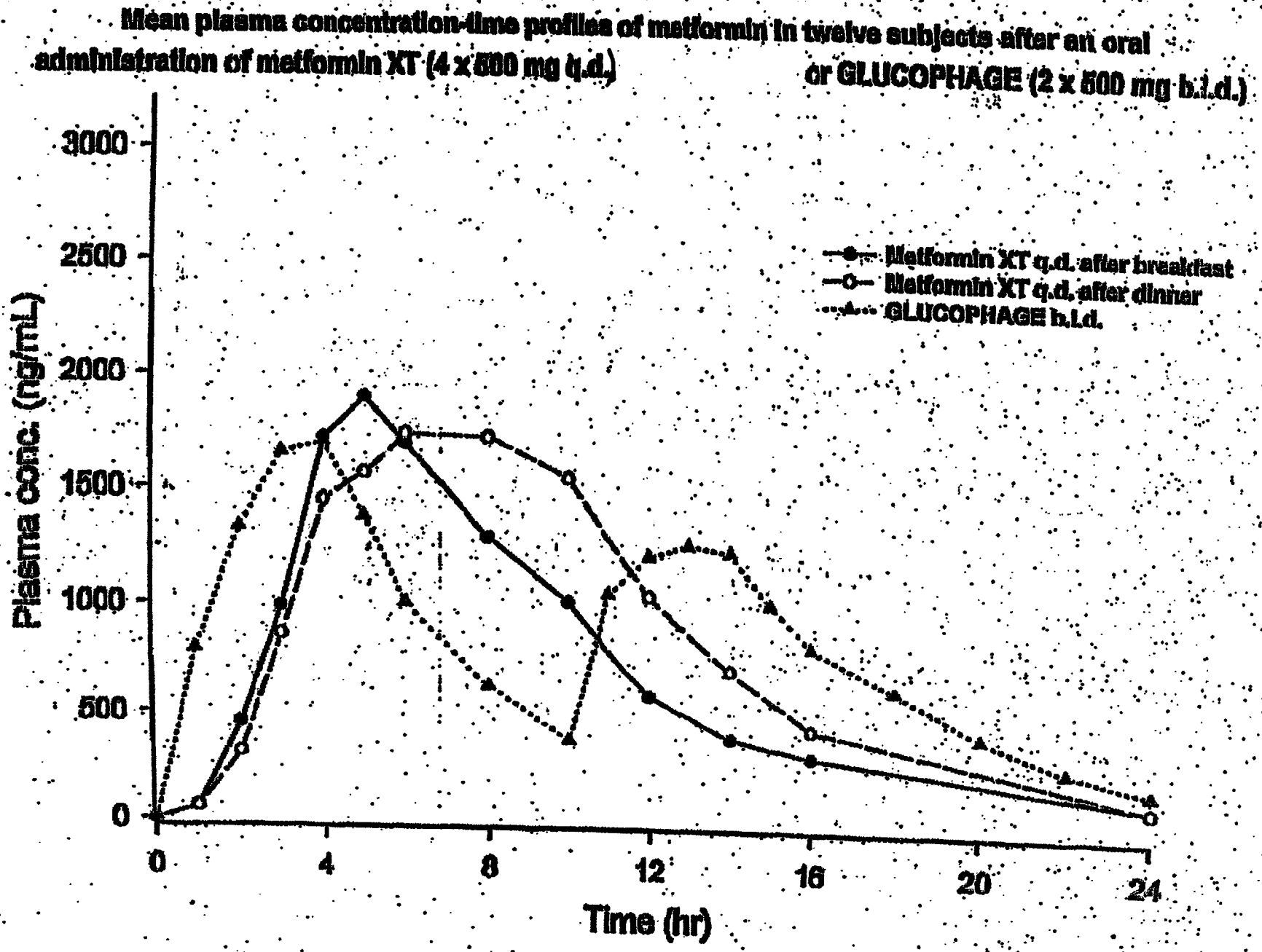


FIGURE 3

Mean plasma concentration-time profiles of metformin in eight healthy subjects after multiple oral doses of metformin XT (4 x 500 mg q.d.)

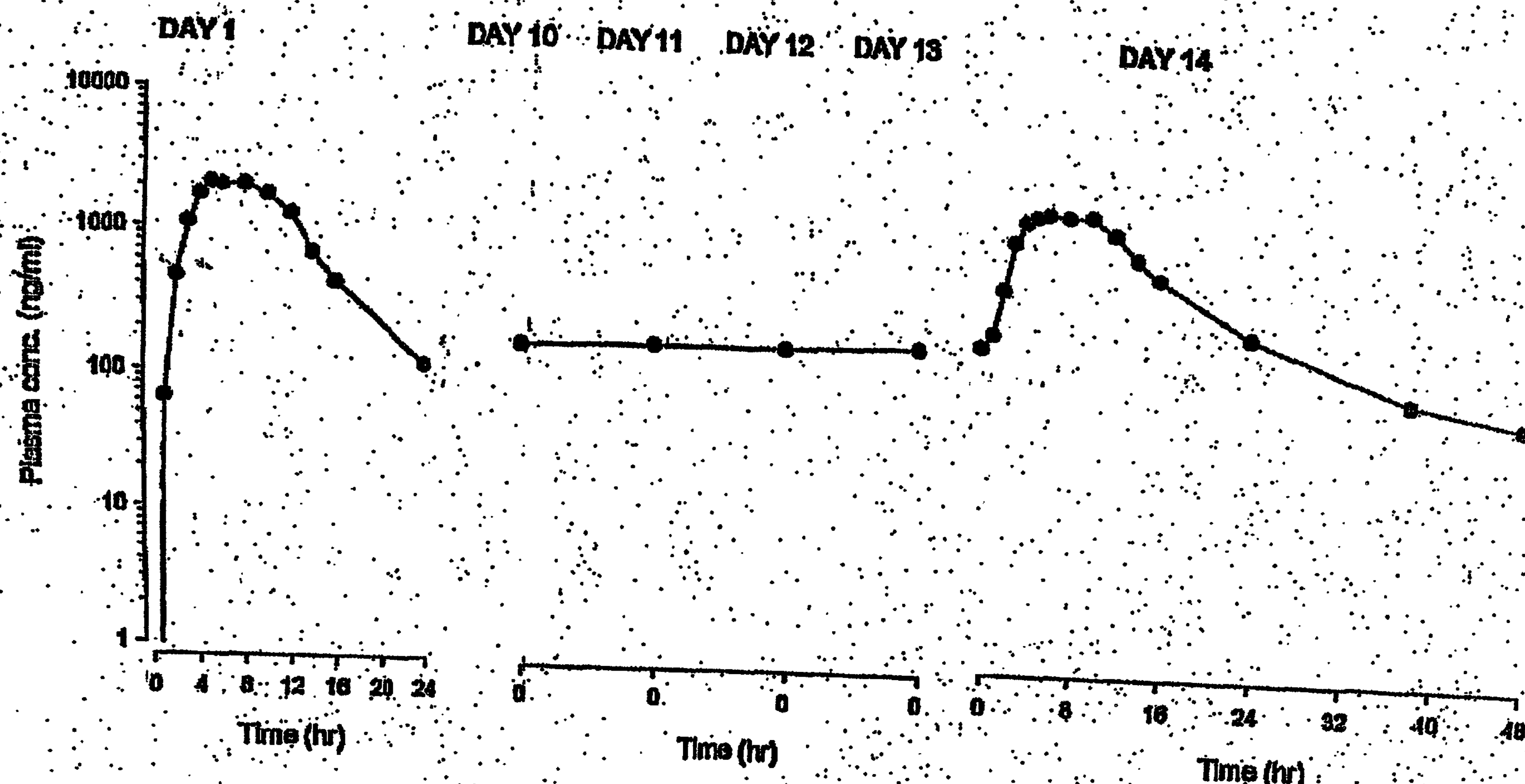


FIGURE 4

Mean steady-state plasma concentration-time profiles of metformin in NIDDM patients (n=23) after multiple oral doses of metformin XT (2 x 1000 mg, q.d. with dinner) or GLUCOPHAGE (1 x 1000 mg, b.i.d.) for 4 weeks

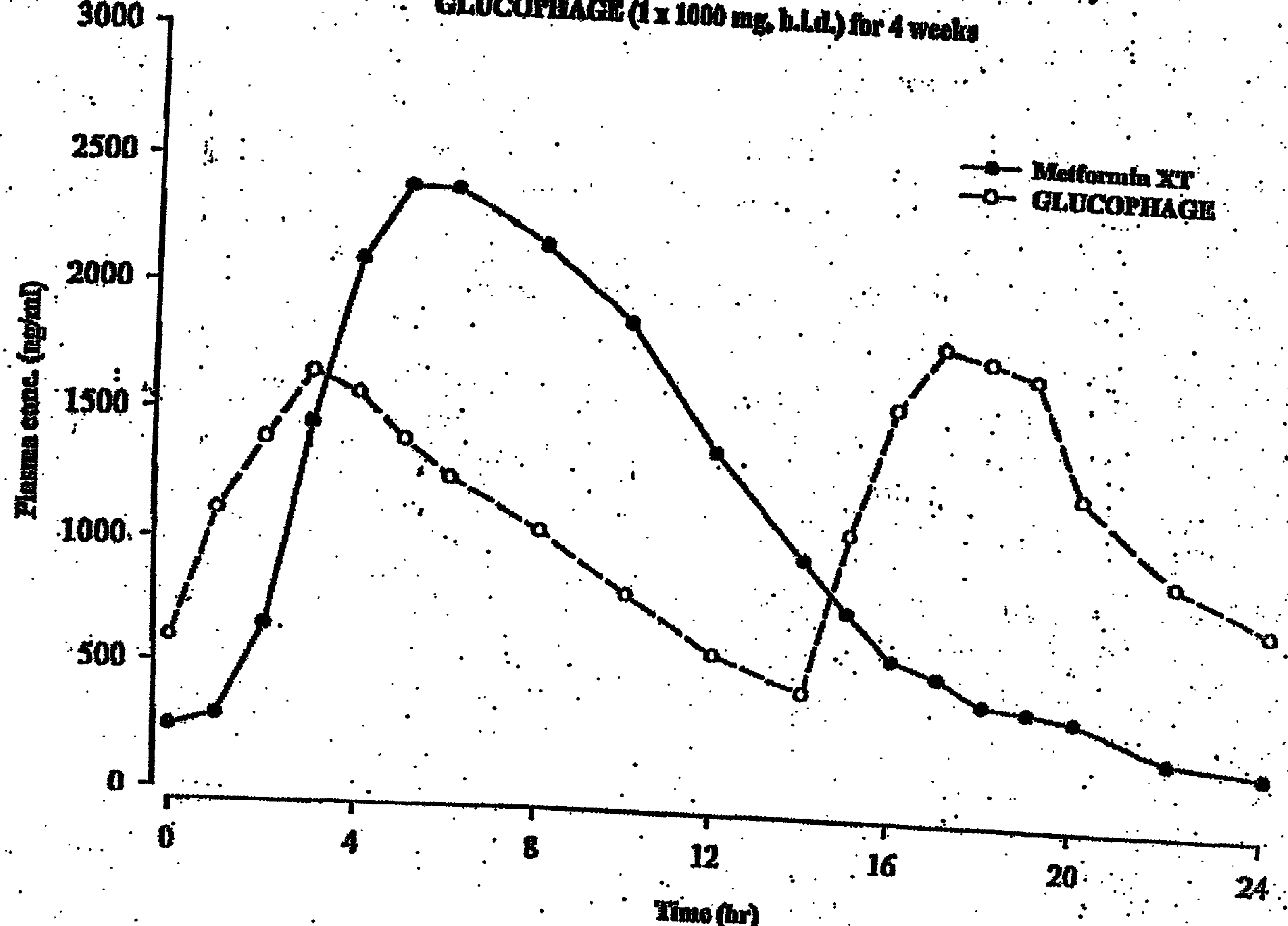
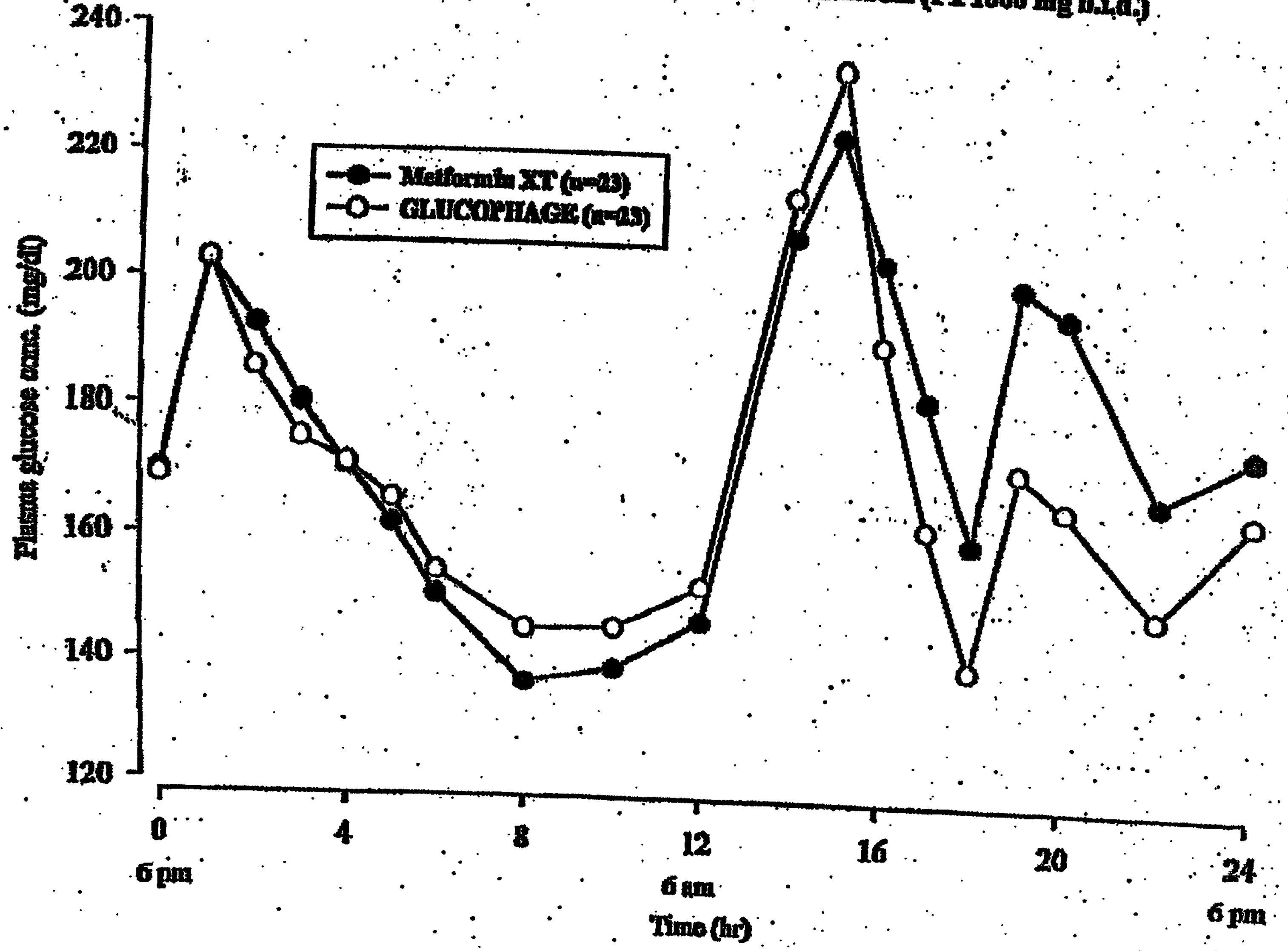


FIGURE 5

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.)



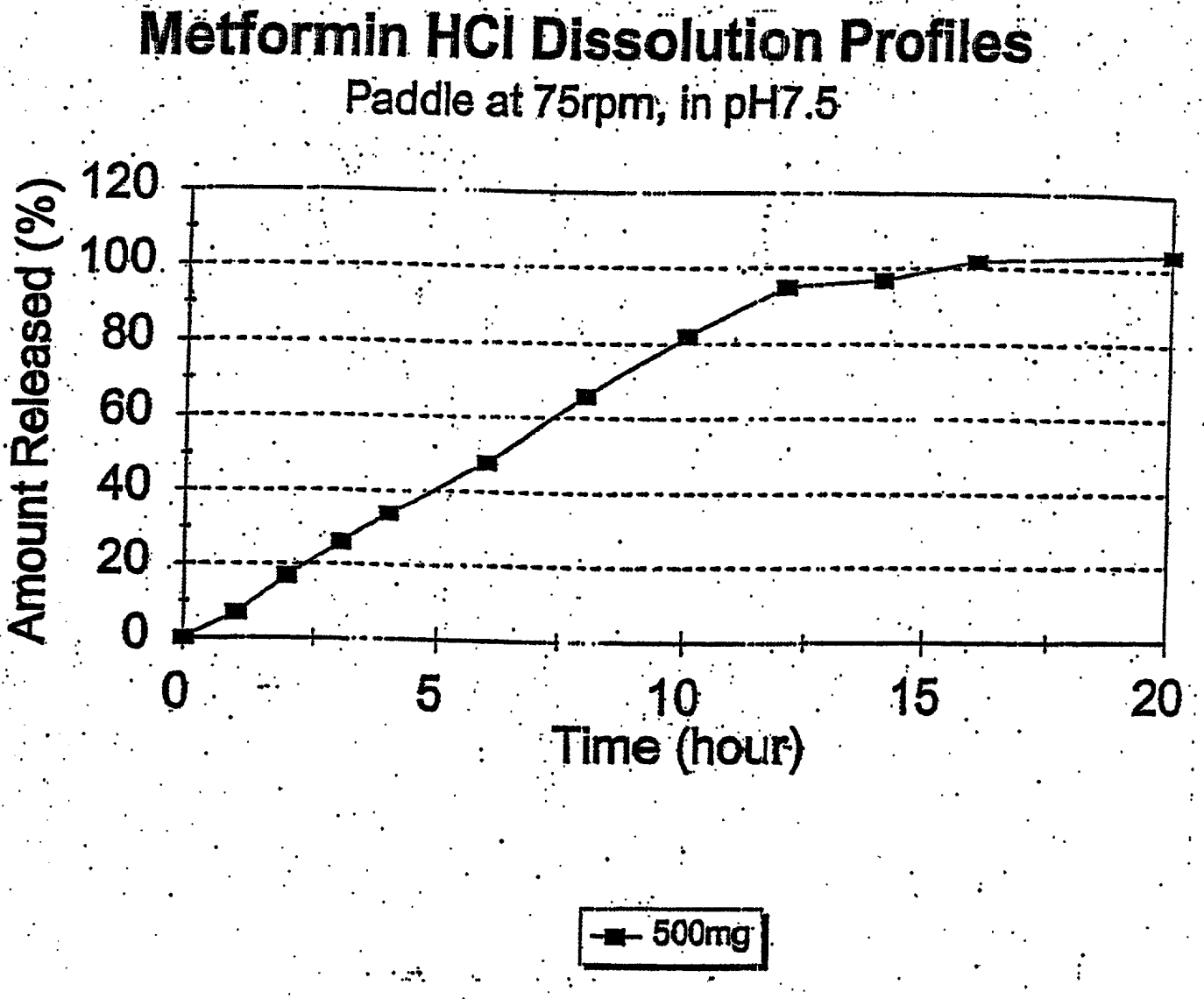

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
500mg

FIGURE 6

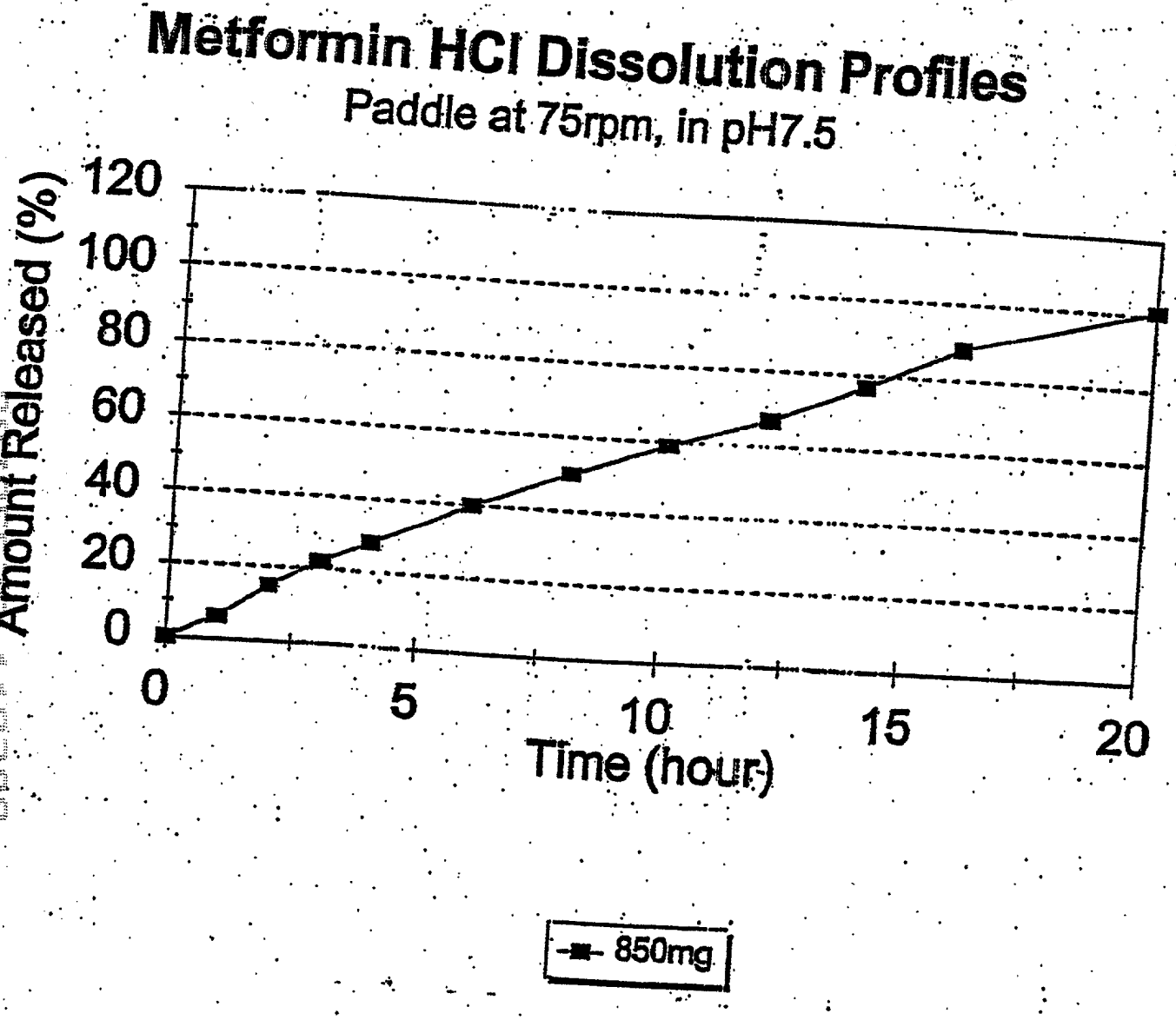

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
850mg

FIGURE 7

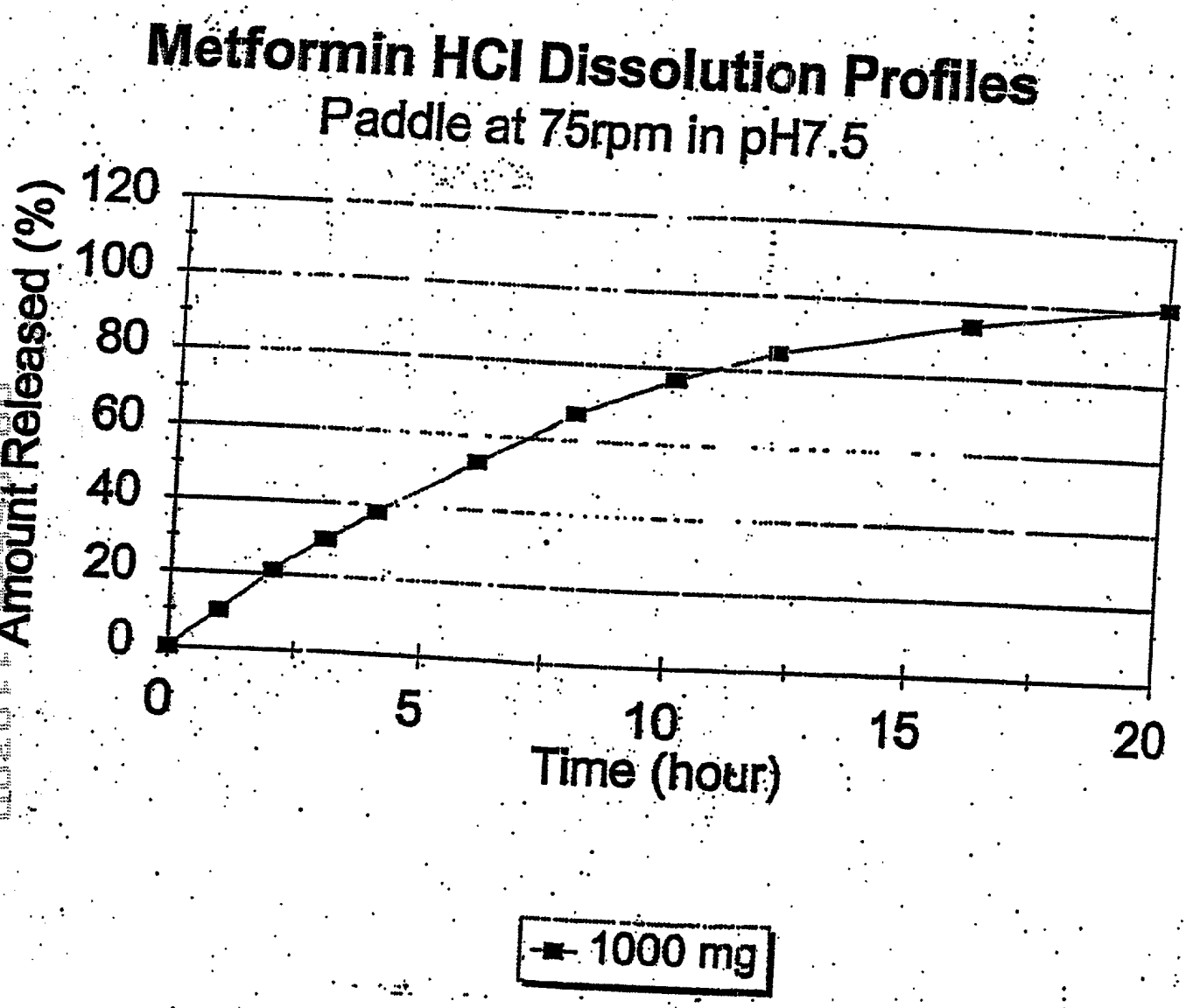

Metformin HCl Dissolution Profiles
Paddle at 75rpm in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
1000 mg

FIGURE 8

Express Mail Label No. EL 415 728 697 US

11-06-00

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012

Total Pages in this Submission
55

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

and invented by:

Xiu Xiu CHENG, Chih-Ming CHEN, Steve JAN and Joseph CHOU

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Enclosed are:

Application Elements

1. ☐ Filing fee as calculated and transmitted as described below

2. ☒ Specification having 42 pages and including the following:

   a. ☒ Descriptive Title of the Invention
   b. ☐ Cross References to Related Applications *(if applicable)*
   c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   d. ☐ Reference to Microfiche Appendix *(if applicable)*
   e. ☒ Background of the Invention
   f. ☒ Brief Summary of the Invention
   g. ☒ Brief Description of the Drawings *(if drawings filed)*
   h. ☒ Detailed Description
   i. ☒ Claim(s) as Classified Below
   j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   - a. ☐ Formal Number of Sheets _____
   - b. ☒ Informal Number of Sheets 8

4. ☐ Oath or Declaration
   - a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   - b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   - c. ☐ With Power of Attorney ☐ Without Power of Attorney
   - d. ☐ *DELETION OF INVENTOR(S)*
     Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche *(Appendix)*

7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
   - a. ☐ Paper Copy
   - b. ☐ Computer Readable Copy *(identical to computer copy)*
   - c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*

9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☒ Acknowledgment postcard

14. ☒ Certificate of Mailing
    - ☐ First Class ☒ Express Mail *(Specify Label No.):* EL 415 728 697 US

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

17. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	34	- 20 =	14	x	$18.00	$252.00
Indep. Claims	2	- 3 =	0	x	$80.00	$0.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$710.00
OTHER FEE *(specify purpose)* _____						$0.00
					TOTAL FILING FEE	$962.00

☐ A check in the amount of to cover the filing fee is enclosed.

☐ The Commissioner is hereby authorized to charge and credit Deposit Account No. as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☐ Credit any overpayment.
- ☐ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Signature

Robert J. Paradiso
Reg. No. 41,240

Dated: **November 3, 2000**

23280
PATENT_TRADEMARK OFFICE

cc:

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

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

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

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:

(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

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_{0-24hr} 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_{0-24hr} from at least 80%, preferably at least 90% of the mean AUC_{0-24} 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

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

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

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.

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.

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.

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.

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

(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.

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

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.

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

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%

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

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.

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.

(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).

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.

(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).

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.

(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).

(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.

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:

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

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:

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) 357 (between doses)	882 882	1.8 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.

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

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.

<u>Study 4</u>

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).

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.

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	$AUC_{0\text{-}24hr}$ (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	T_{lag} (hr)	$t_{½}$ (hr)	$AUC_{0\text{-}24hr}$	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.

WHAT IS CLAIMED IS:

1. A method for 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 at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration.

2. The controlled release dosage form of claim 1 wherein said at least one antihyperglycemic agent 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 method of claim 3, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 5.5 to 7.0 hours after the administration.

6. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at breakfast and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 6.0 to about 7.5 hours after the administration.

7. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

8. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

9. The method of claim 3, in which the administration of the at east one metformin dosage form 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 administration.

10. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

11. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

12. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

13. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

14. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from 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.

15. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ that is from at least 90% 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.

16. The method of claim 3, in which the once-a-day dose of the metformin is administered at dinner.

17. The method of claim 16, in which the once-a-day dose of metformin is administered at fed state.

18. The method of claim 16, in which the once-a-day dose of the metformin is about 2000 mg, which is provided by two controlled release dosage forms containing about 1000 mg metformin each.

19. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

20. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

21. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

22. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

23. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

24. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

25. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set

forth in FIG. 6, based on administration of a 2000 mg once-a-day dose of metformin at breakfast.

26. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma glucose concentration-time profile substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

27. The method of claim 3, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. The method of claim 3, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. The method of claim 3, in which the dose of metformin comprises metformin hydrochloride.

30. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 1000 mg to about 2500 mg.

31. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 2000 mg to about 2500 mg metformin.

32. A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering 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 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.

33. The method of claim 32 wherein said dosage form maintains bioavailability from at least 80% of the immediate release composition.

34. The method of claim 32 wherein said dosage form maintains bioavailability from aat least 90% of the immediate release composition.

ABSTRACT

A method 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 a 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.

FIGURE 1

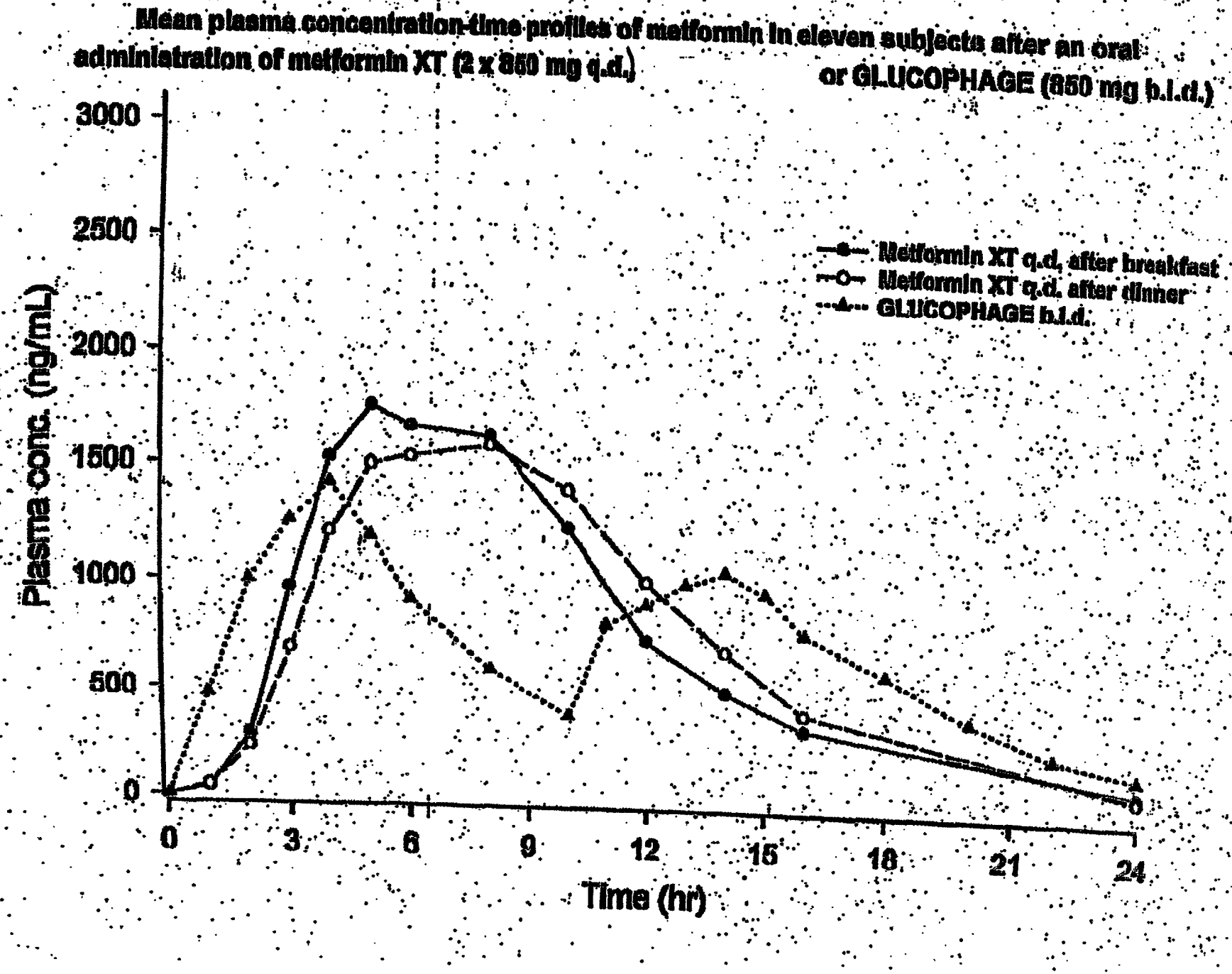


FIGURE 2

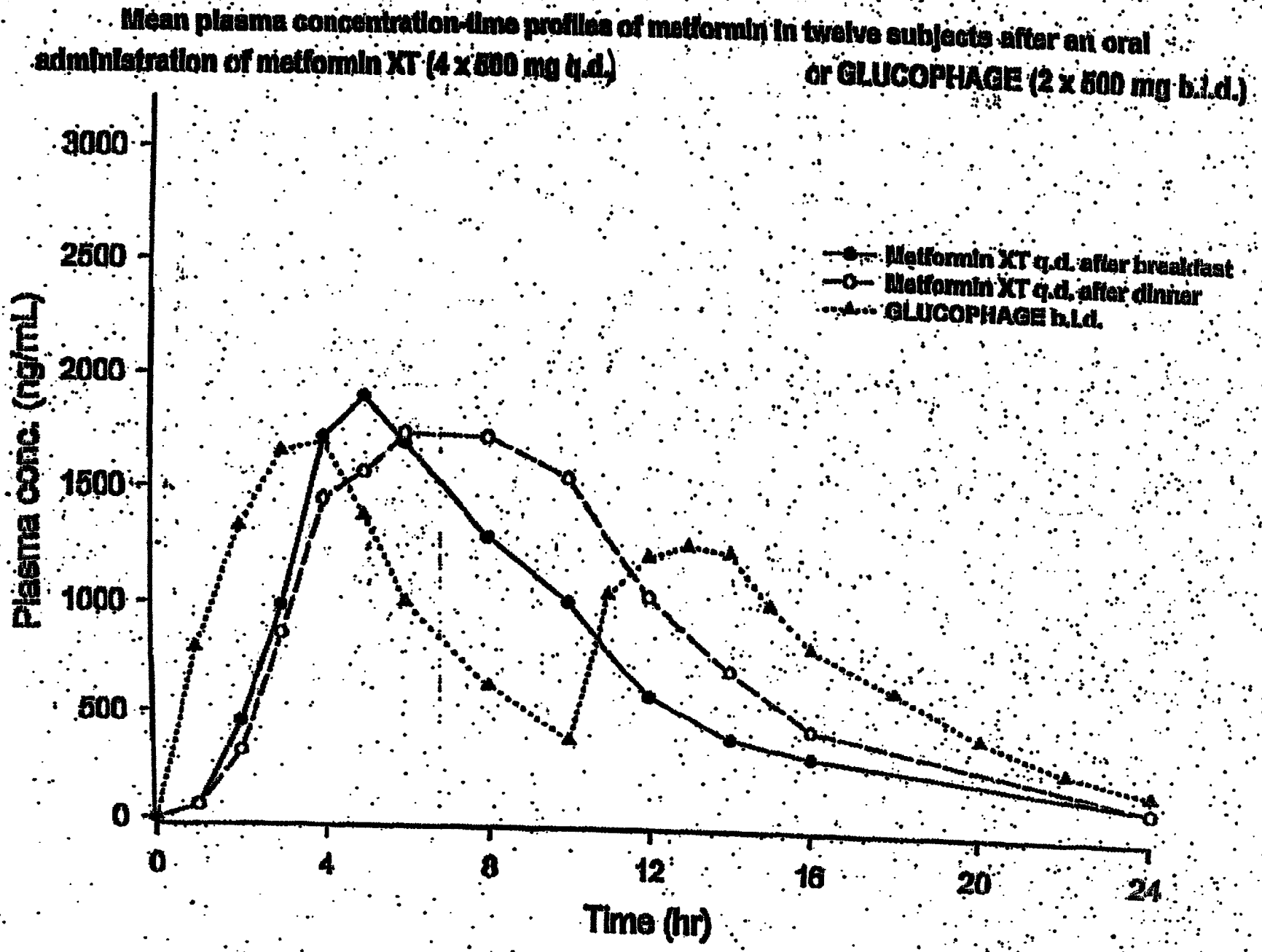


FIGURE 3

Mean plasma concentration-time profiles of metformin in eight healthy subjects after multiple oral doses of metformin XT (4 x 500 mg q.d.)

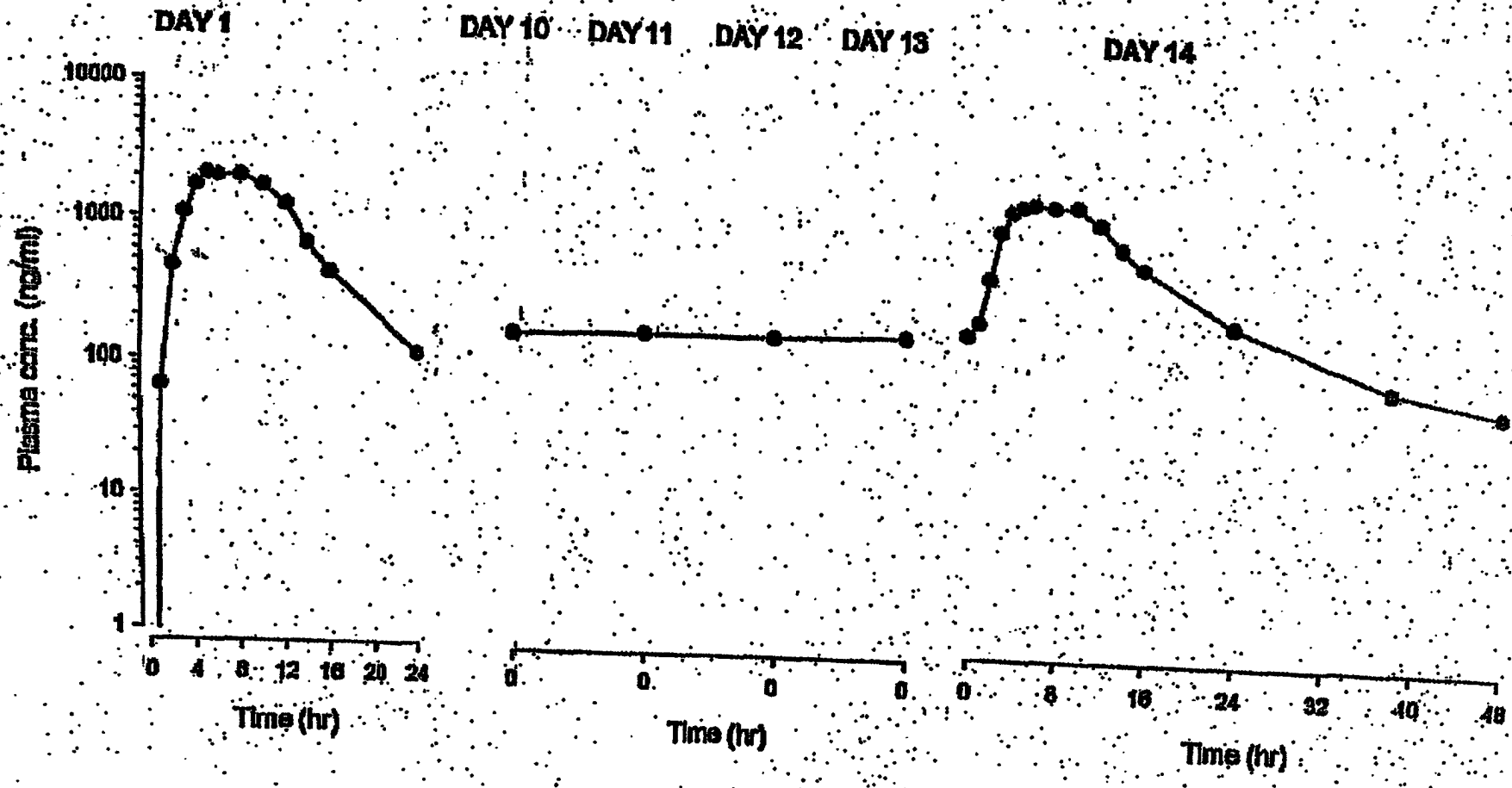


FIGURE 4

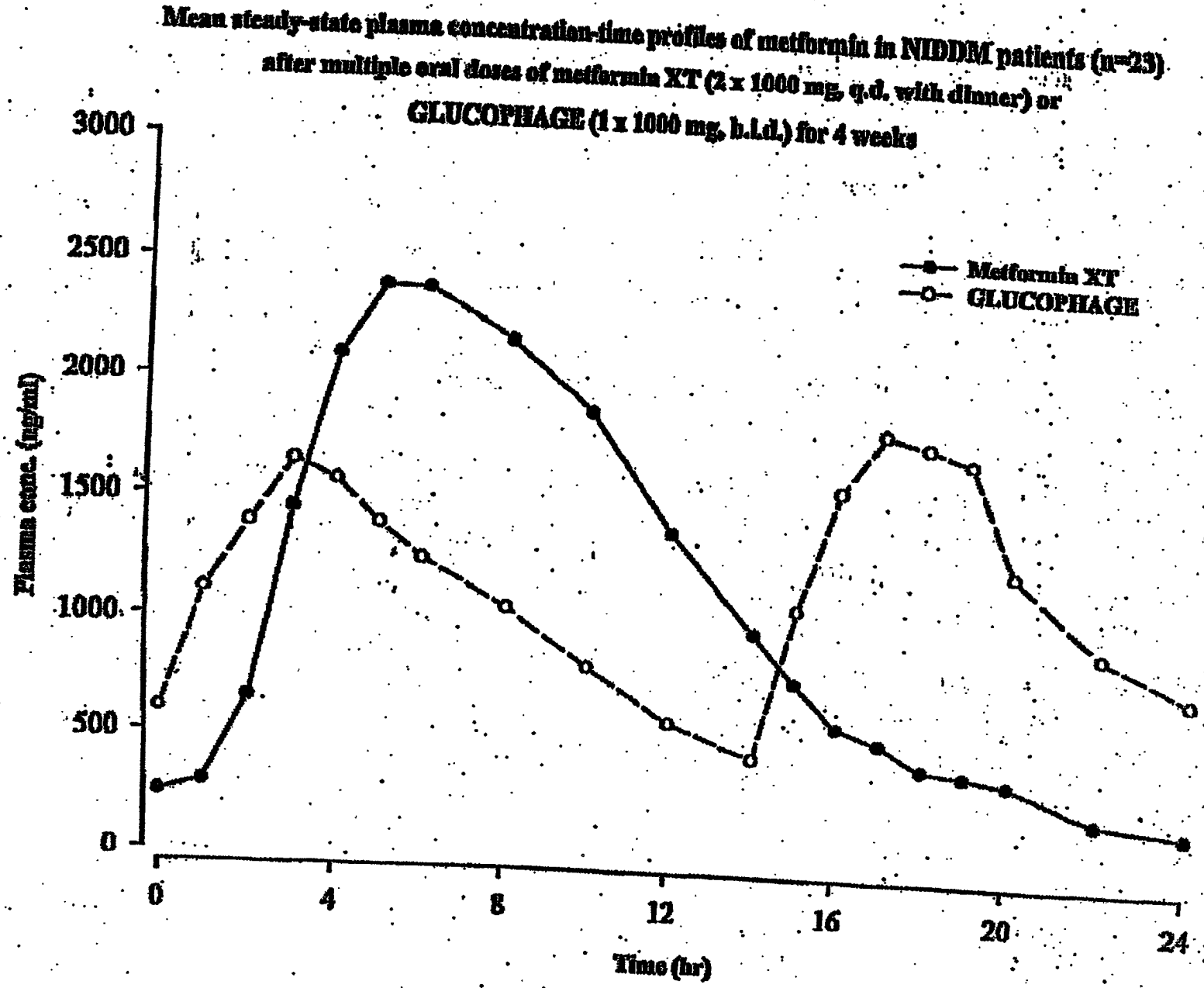
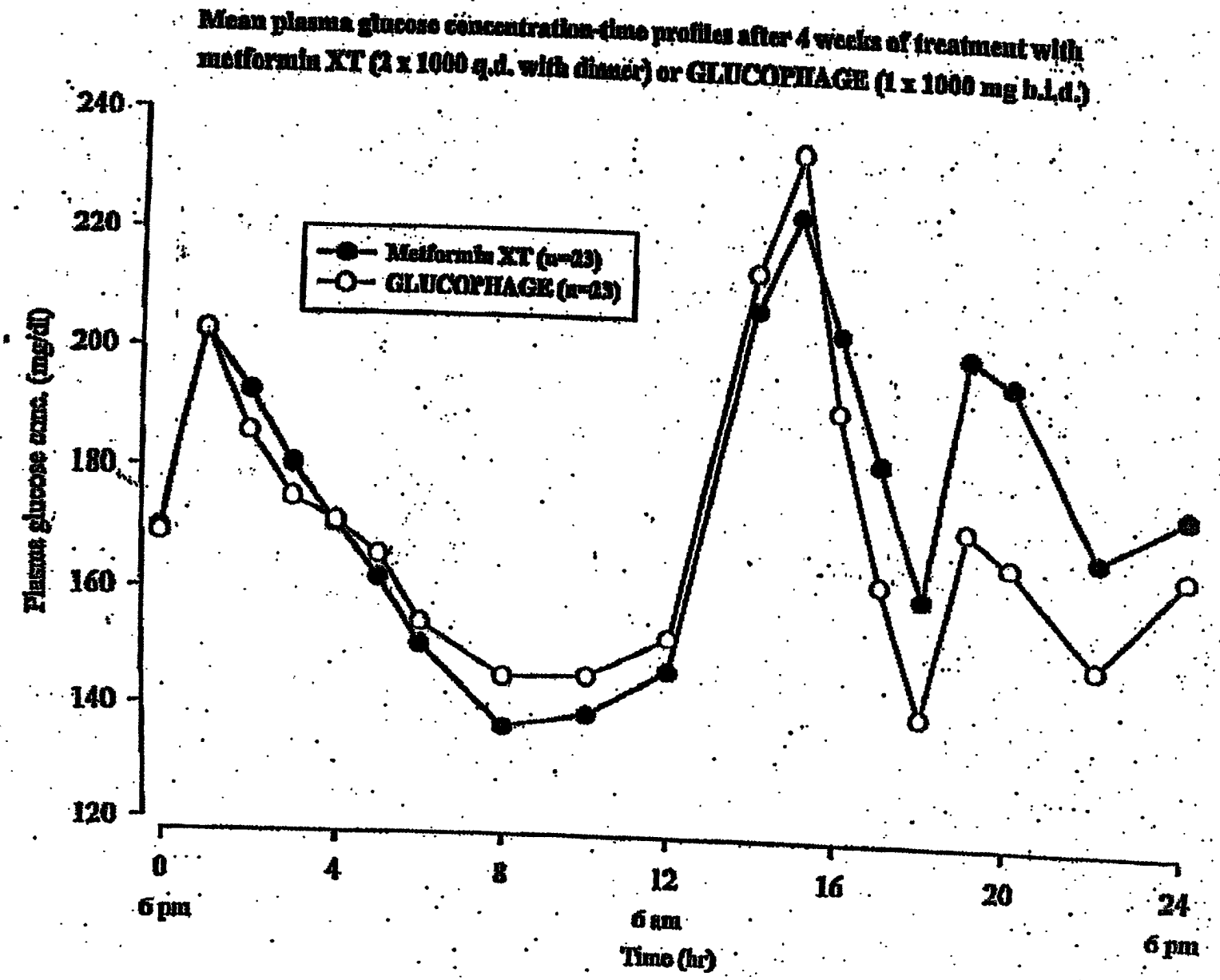


FIGURE 5



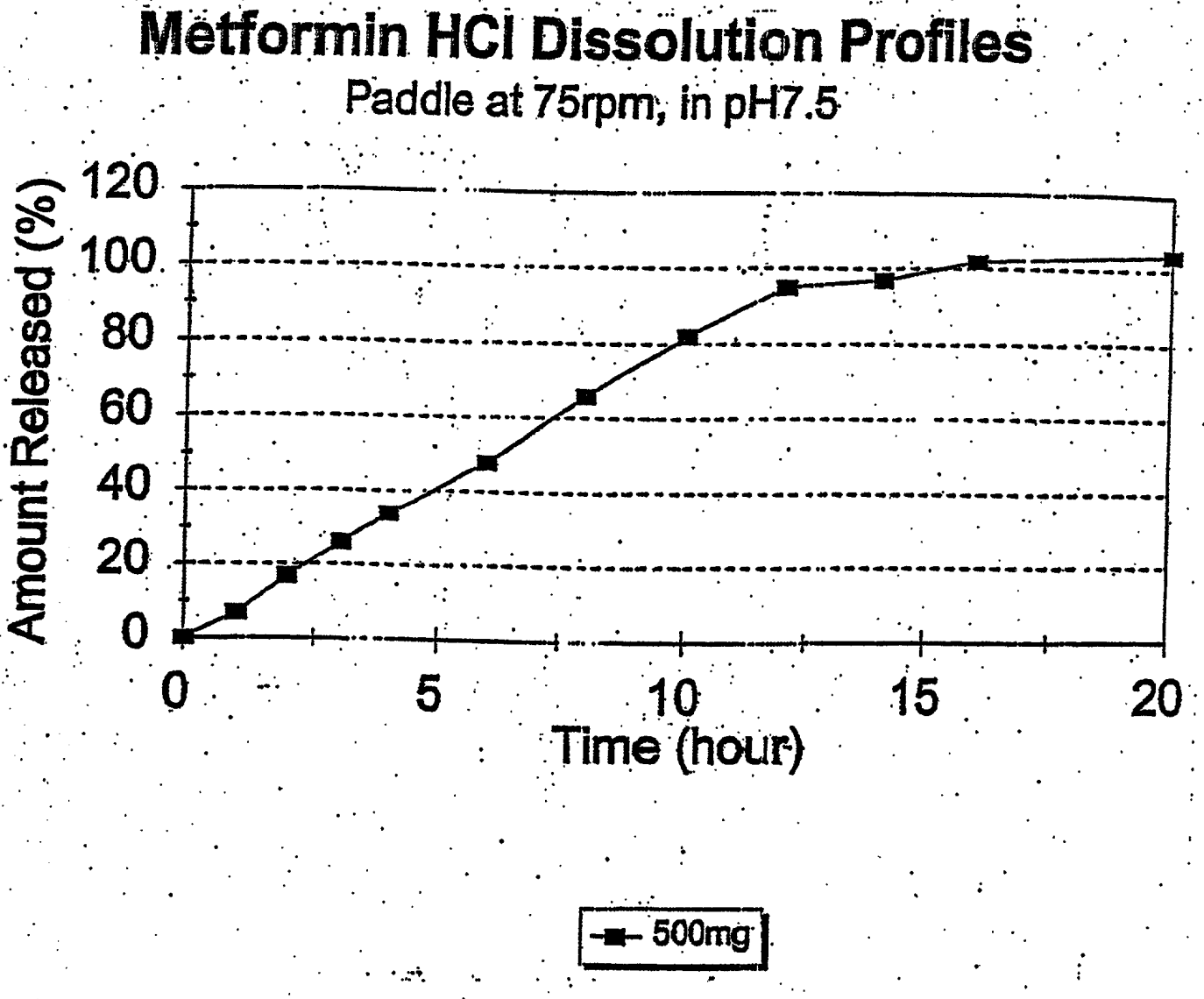

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
500mg

FIGURE 6

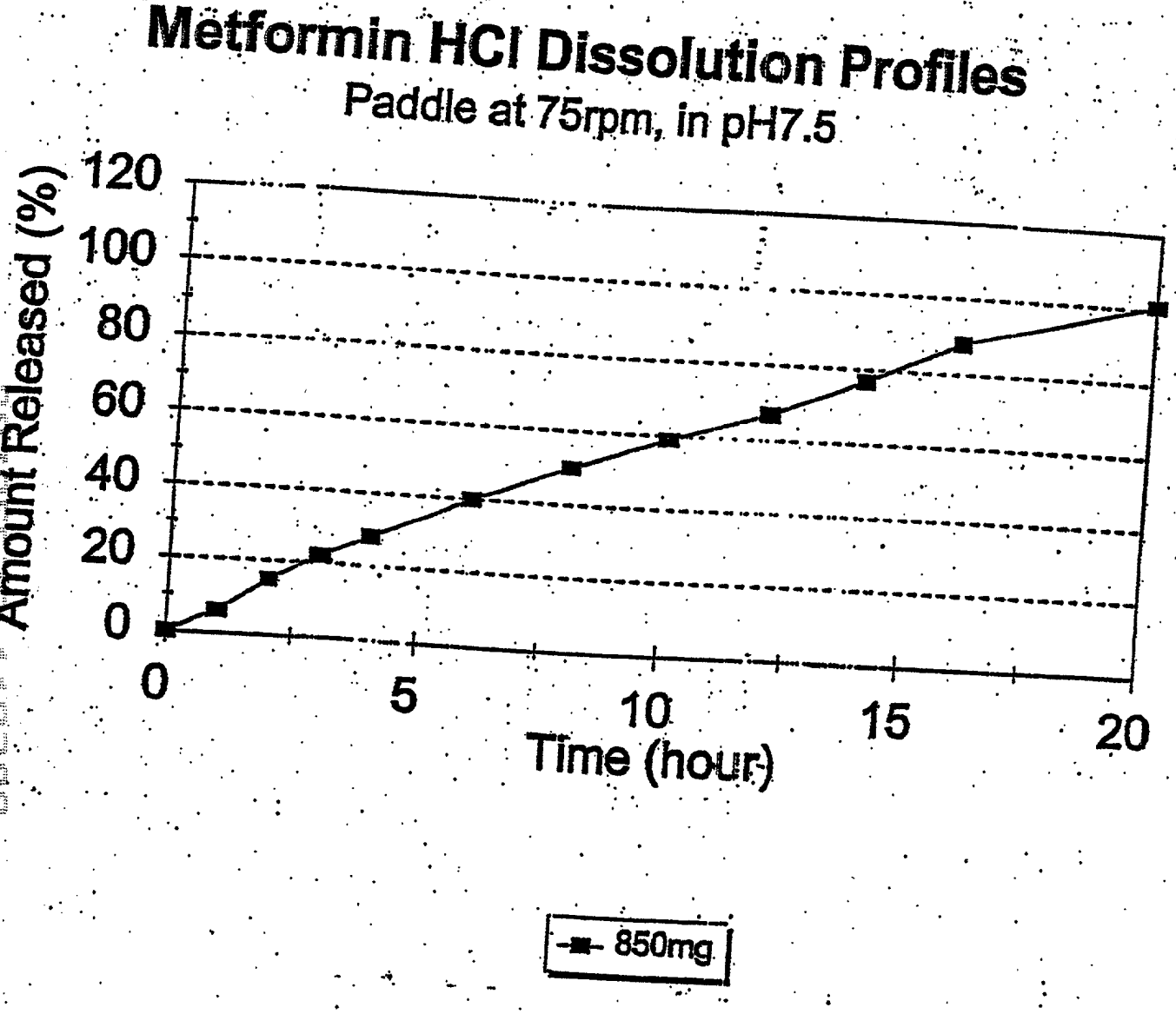

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
850mg

FIGURE 7

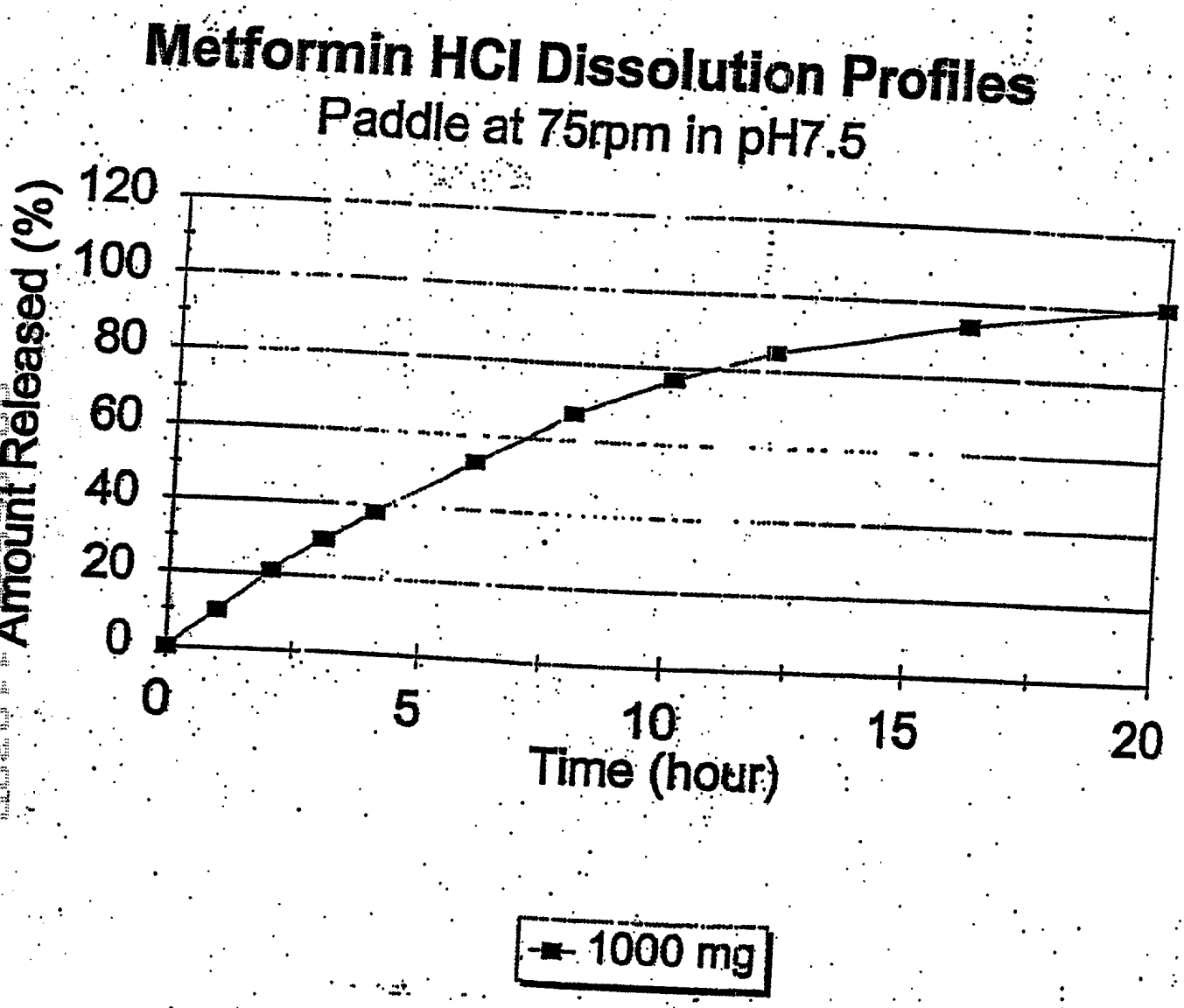

Metformin HCl Dissolution Profiles
Paddle at 75rpm in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
1000 mg

FIGURE 8

Subclass	ISSUE CLASSIFICATION
Class	

PATENT NUMBER

U.S. UTILITY Patent Application

O.A.P.E.	PATENT DATE
CLASS/SUB 514 2 G.A. 1615	

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/705625		424	468	1615	WARE

APPLICANTS

Xiu Xiu Cheng
Chih-Ming Chen
Steve Jan
Joseph Chou

TITLE

Methods for treating diabetes via administratrion of controlled release metformin

PTO-2040
12/99

ISSUING CLASSIFICATION

ORIGINAL

CLASS	SUBCLASS

INTERNATIONAL CLASSIFICATION

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER

☐ The term of this patent subsequent to _____ (date) has been disclaimed.

☐ The term of this patent shall not extend beyond the expiration date of U.S. Patent No. _____

☐ The terminal ___ months of this patent have been disclaimed.

DRAWINGS		
Sheets Drwg.	Figs. Drwg.	Print Fig.

_____ (Assistant Examiner) _____ (Date)

_____ (Primary Examiner) _____ (Date)

_____ (Legal Instruments Examiner) _____ (Date)

CLAIMS ALLOWED	
Total Claims	Print Claim for O.G.

NOTICE OF ALLOWANCE MAILED

ISSUE FEE

Amount Due	Date Paid

ISSUE BATCH NUMBER

WARNING:
The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A
(Rev. 6/99)

FILED WITH: ☐ DISK (CRF) ☐ FICHE ☐ CD-ROM
(Attached to packet on right inside flap)

[redacted]

SEARCHED

Class	Sub.	Date	Exmr.
424	473	12-2001	TW
	468		
	474		
	475		
	479		
	480		
	482		
514	635		
	588		
	591		
	592		
	593		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

Inventor Search	Date	Exmr.
BRS	12-20-01	TW

(RIGHT OUTSIDE)

ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION		71476 =	1/24/01
O.I.P.E. CLASSIFIER			11/29/01
FORMALITY REVIEW		69652	
RESPONSE FORMALITY REVIEW	JS	69134	4-13-01

INDEX OF CLAIMS

✔ ..... Rejected
= ..... Allowed
– (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim Final	Claim Original	Date
	1	1/24/01
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
	13	
	14	
	15	
	16	
	17	
	18	
	19	
	20	
	21	
	22	
	23	
	24	
	25	
	26	
	27	
	28	
	29	
	30	
	31	
	32	
	33	
	34	1
	35	
	36	
	37	
	38	
	39	
	40	
	41	
	42	
	43	
	44	
	45	
	46	
	47	
	48	
	49	
	50	

Claim Final	Claim Original	Date
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

Claim Final	Claim Original	Date
	101	
	102	
	103	
	104	
	105	
	106	
	107	
	108	
	109	
	110	
	111	
	112	
	113	
	114	
	115	
	116	
	117	
	118	
	119	
	120	
	121	
	122	
	123	
	124	
	125	
	126	
	127	
	128	
	129	
	130	
	131	
	132	
	133	
	134	
	135	
	136	
	137	
	138	
	139	
	140	
	141	
	142	
	143	
	144	
	145	
	146	
	147	
	148	
	149	
	150	

If more than 150 claims or 10 actions staple additional sheet here

(LEFT INSIDE)

Express Mail Label No. EL 415 728 697 US

11-06-00

11/03/00 EL415728697 U.S. PTO

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012

Total Pages in this Submission
55

11/03/00 U.S. PTO 09/705675 Jc925

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

and invented by:

Xiu Xiu CHENG, Chih-Ming CHEN, Steve JAN and Joseph CHOU

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Enclosed are:

Application Elements

1. ☐ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 42 pages and including the following:

   a. ☒ Descriptive Title of the Invention
   b. ☐ Cross References to Related Applications *(if applicable)*
   c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   d. ☐ Reference to Microfiche Appendix *(if applicable)*
   e. ☒ Background of the Invention
   f. ☒ Brief Summary of the Invention
   g. ☒ Brief Description of the Drawings *(if drawings filed)*
   h. ☒ Detailed Description
   i. ☒ Claim(s) as Classified Below
   j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 300.1012
Total Pages in this Submission 55

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal Number of Sheets _____
   b. ☒ Informal Number of Sheets 8
4. ☐ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☐ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche *(Appendix)*
7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy *(identical to computer copy)*
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*
9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.):* **EL 415 728 697 US**

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

17. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012
Total Pages in this Submission
55

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	34	- 20 =	14	x	$18.00	$252.00
Indep. Claims	2	- 3 =	0	x	$80.00	$0.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$710.00
OTHER FEE *(specify purpose)* _____						$0.00
					TOTAL FILING FEE	$962.00

☐ A check in the amount of to cover the filing fee is enclosed.

☐ The Commissioner is hereby authorized to charge and credit Deposit Account No. as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☐ Credit any overpayment.
- ☐ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Signature

Robert J. Paradise
Reg. No. 41,240

Dated: **November 3, 2000**

cc: 23280
PATENT TRADEMARK OFFICE

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Xiu Xiu CHENG, Chih-Ming CHEN, Steve JAN and Joseph CHOU			Docket No. 300.1012
Serial No. Not Yet Known	Filing Date Herewith	Examiner To Be Assigned	Group Art Unit To Be Assigned

Invention: METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

I hereby certify that the following correspondence:

Utility Patent Application with accompanying documents.

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

November 3, 2000
(Date)

Randolph K. McQueen
(Typed or Printed Name of Person Mailing Correspondence)

Randolph K. McQueen
(Signature of Person Mailing Correspondence)

EL 415 728 697 US
("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing.

FIGURE 1

Mean plasma concentration-time profiles of metformin in eleven subjects after an oral administration of metformin XT (2 x 850 mg q.d.) or GLUCOPHAGE (850 mg b.i.d.)

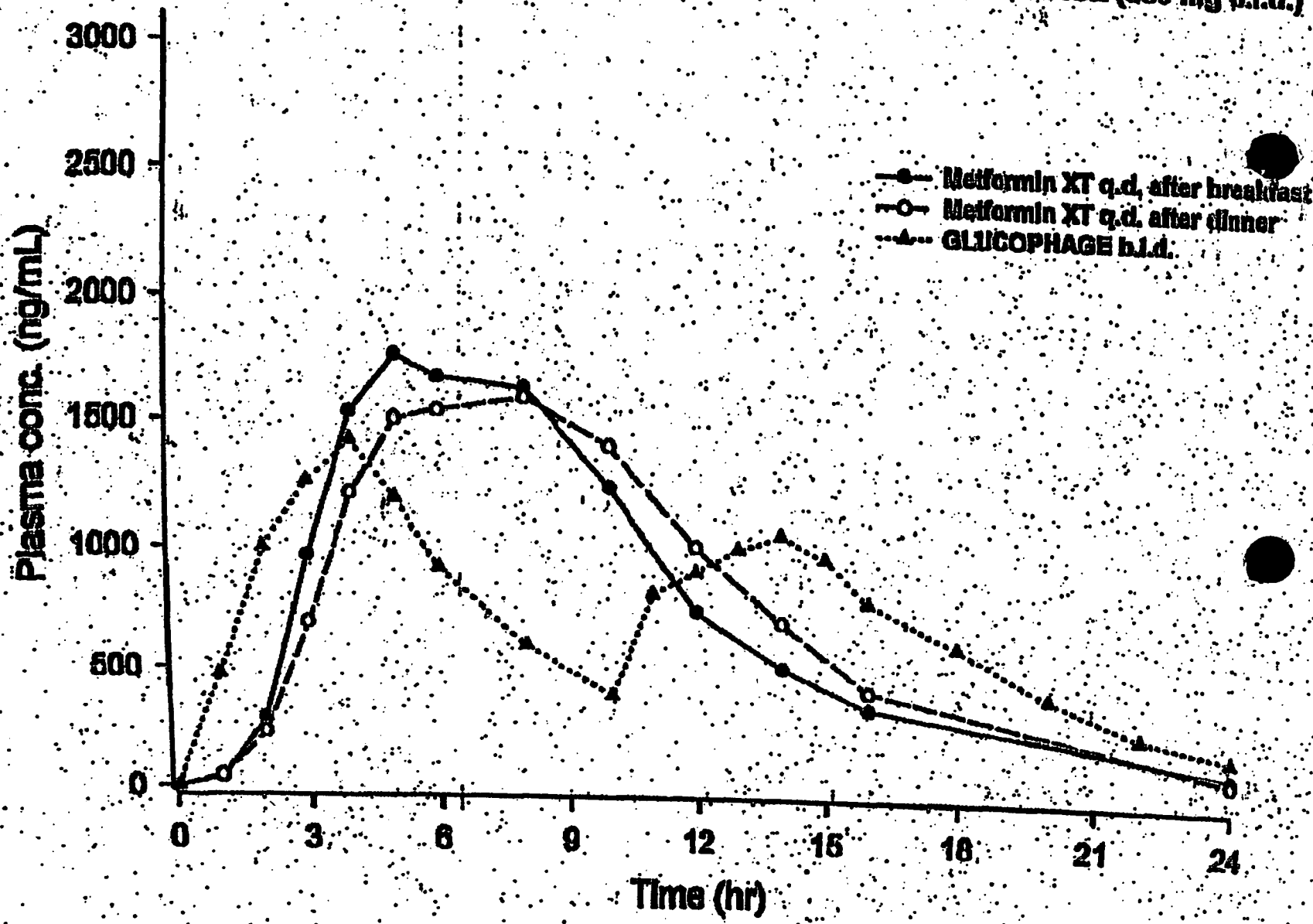


FIGURE 2

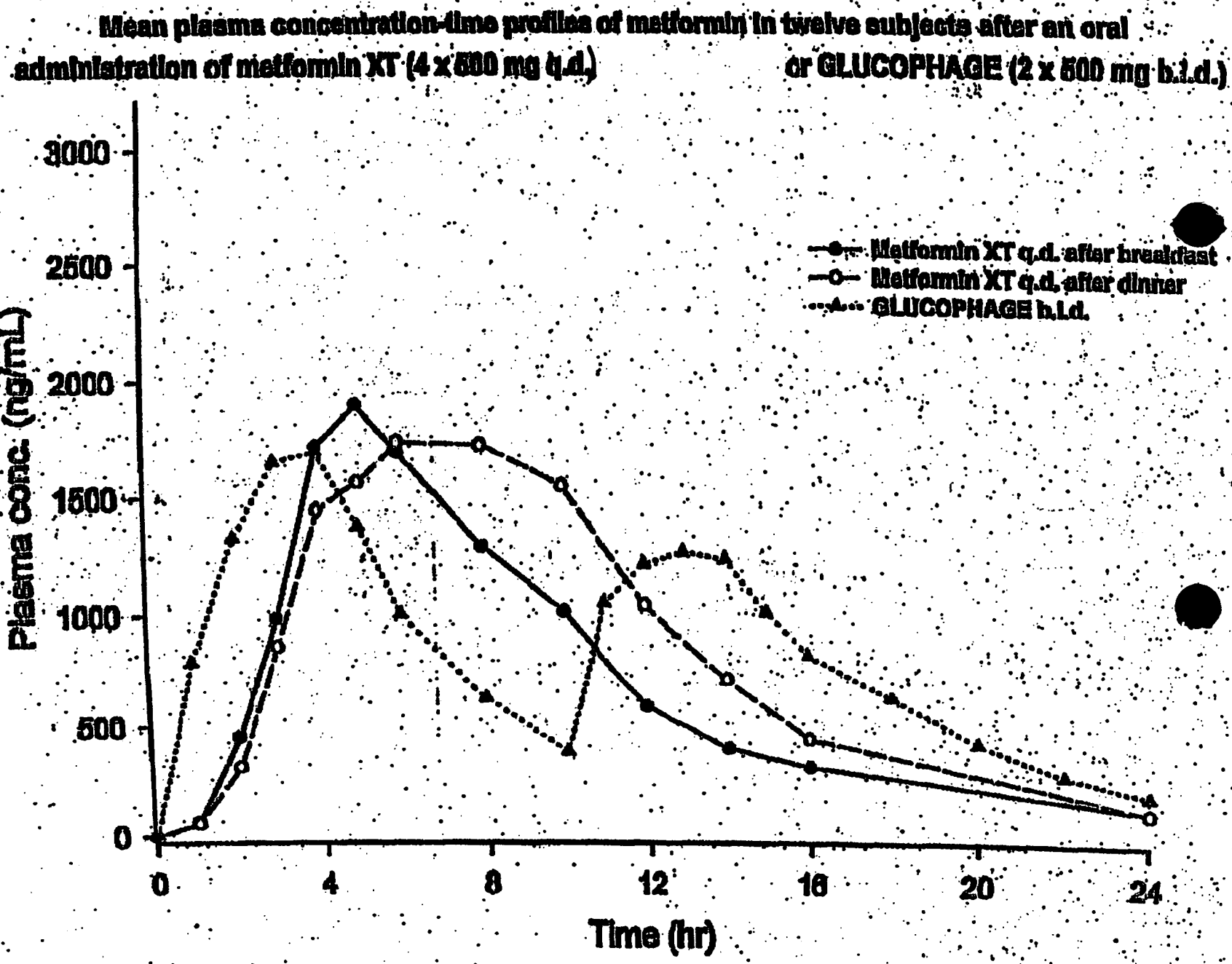


FIGURE 3

Mean plasma concentration-time profiles of metformin in eight healthy subjects after multiple oral doses of metformin XT (4 x 500 mg q.d.)

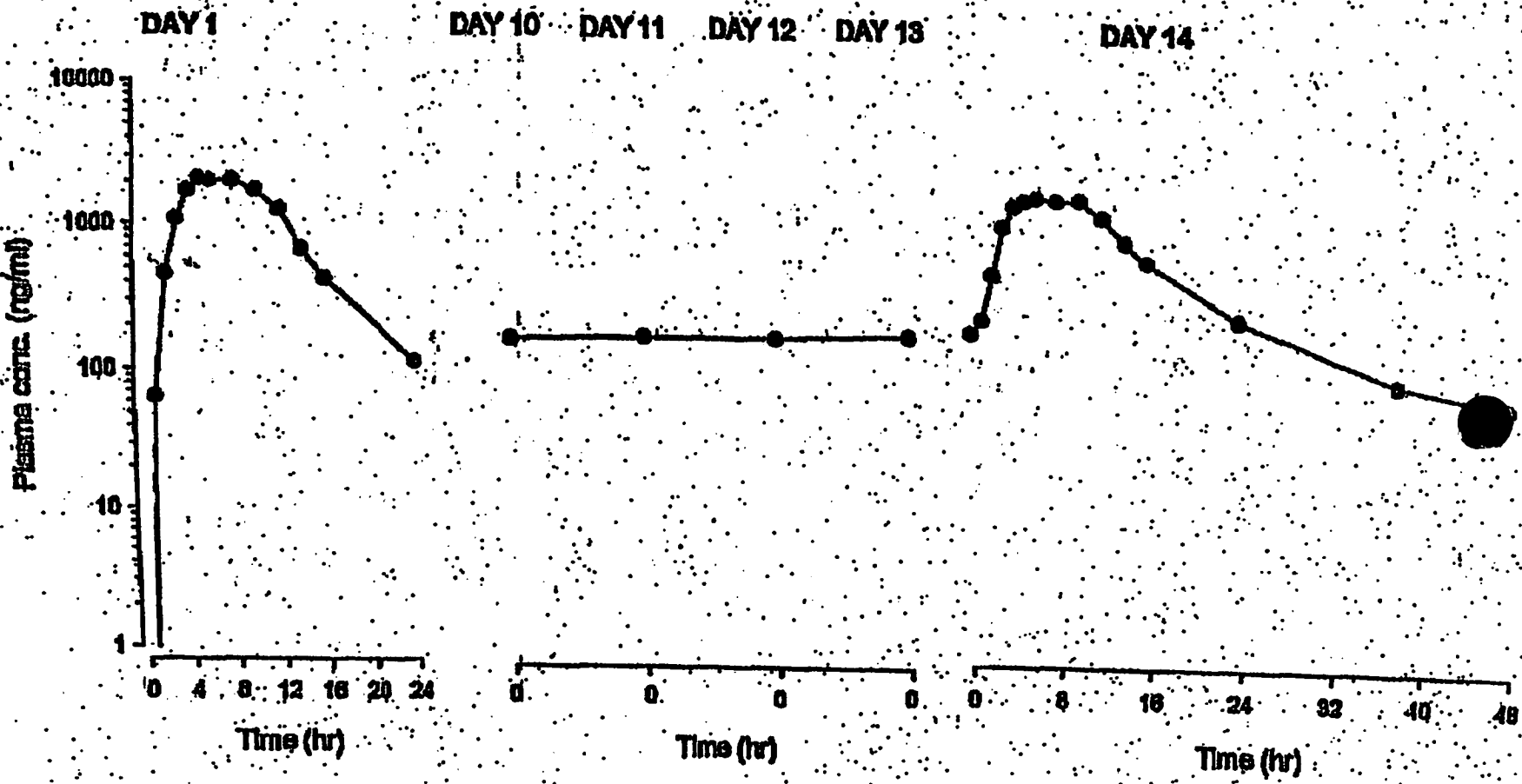


FIGURE 4

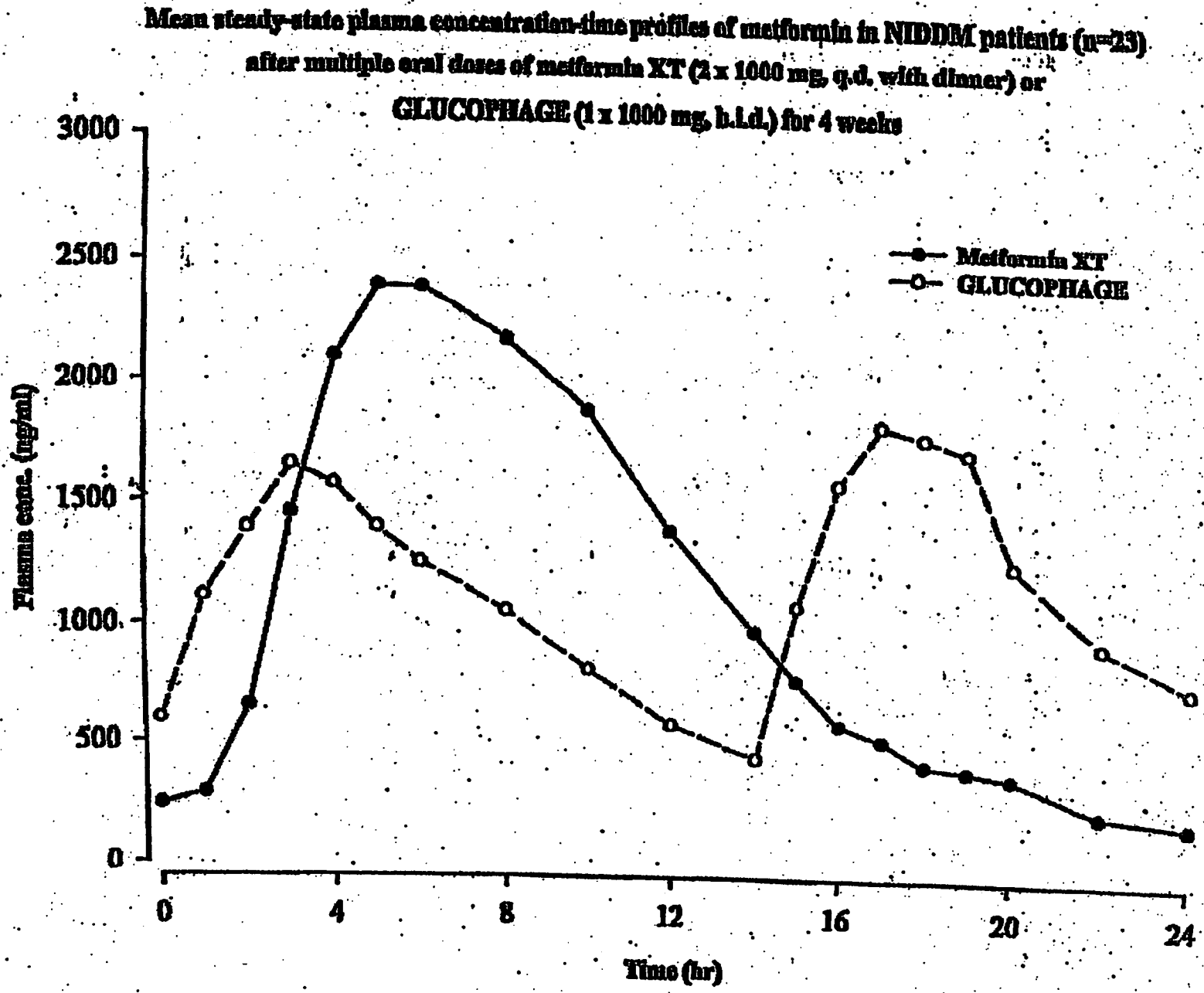
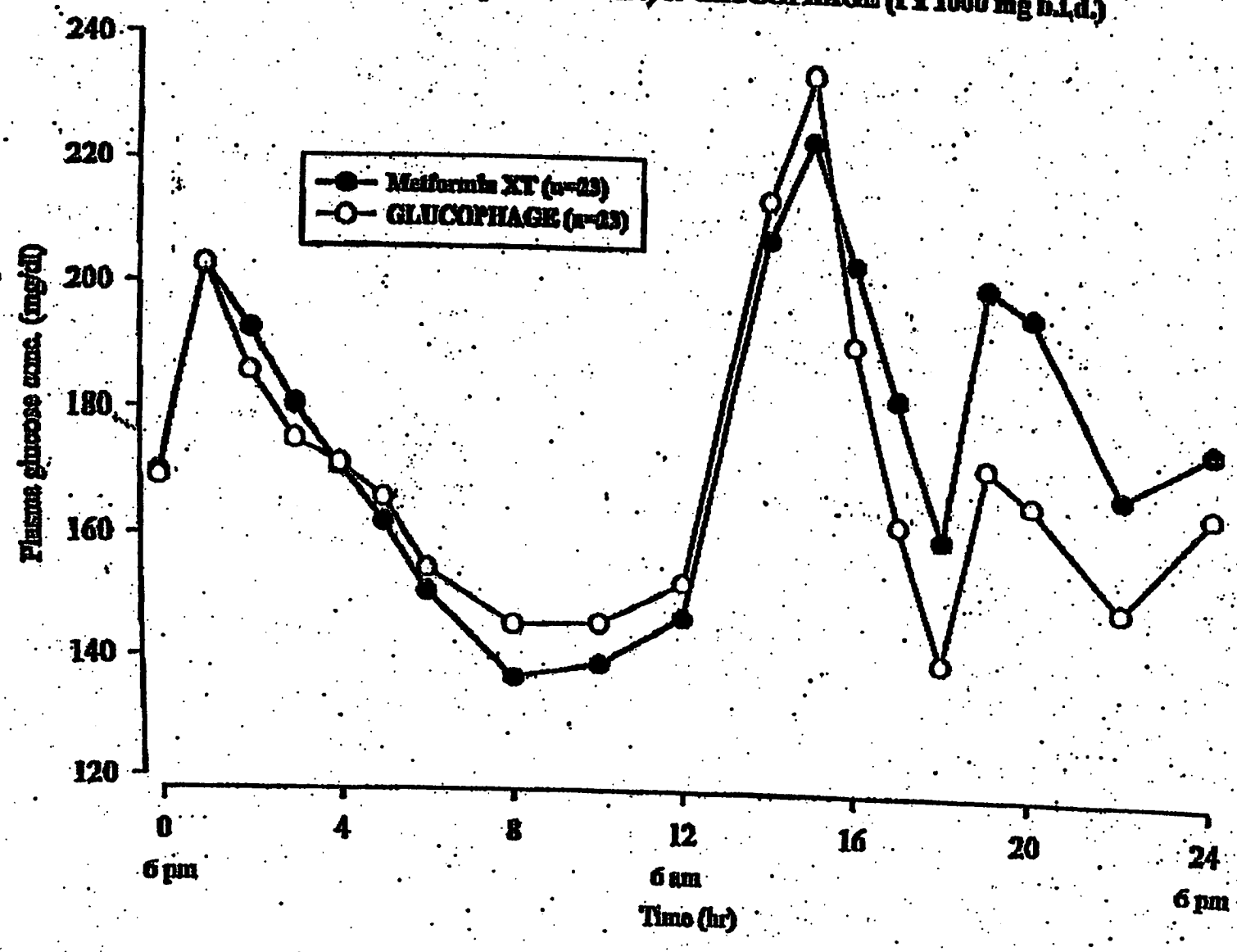


FIGURE 5

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.)



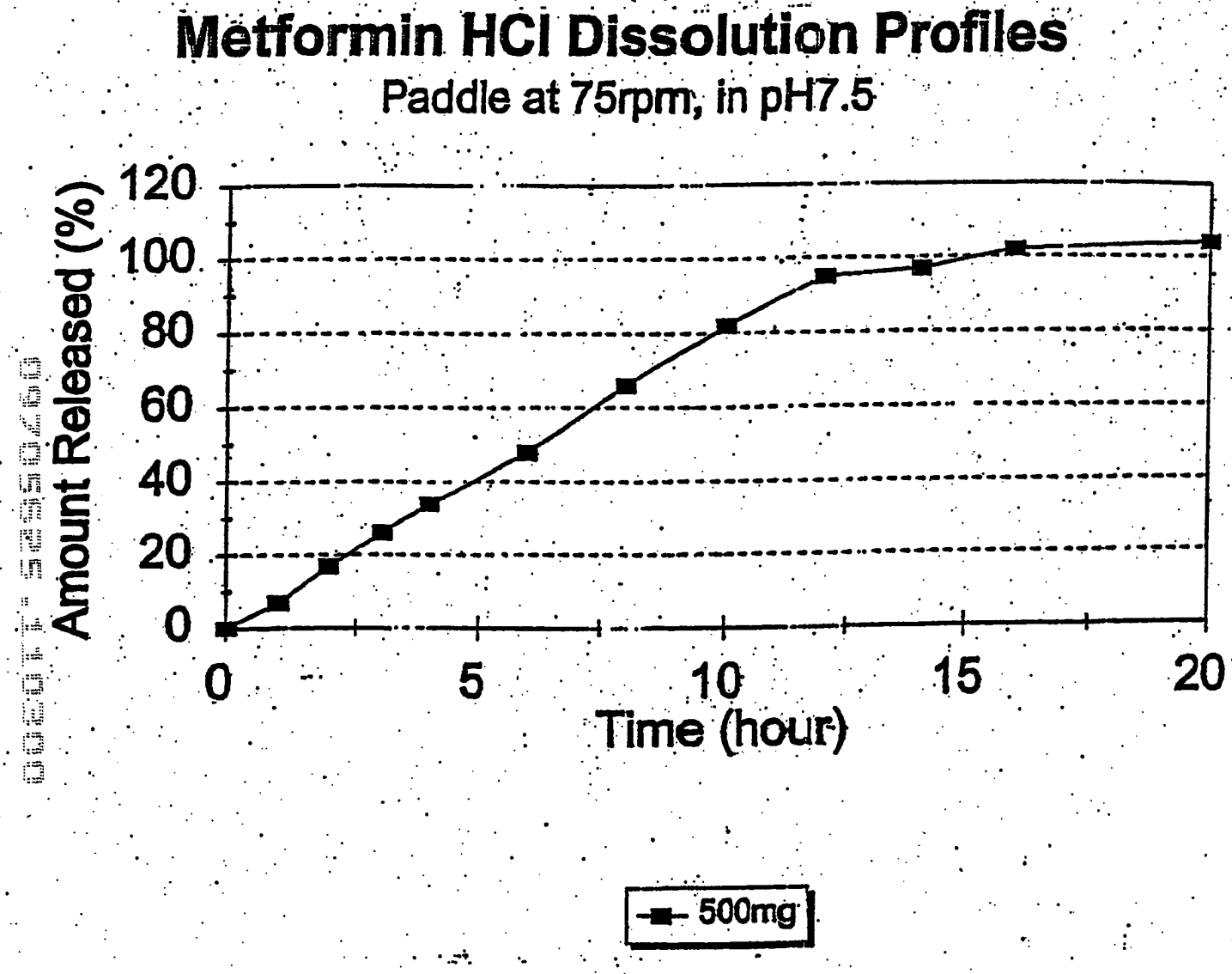

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
500mg

FIGURE 6

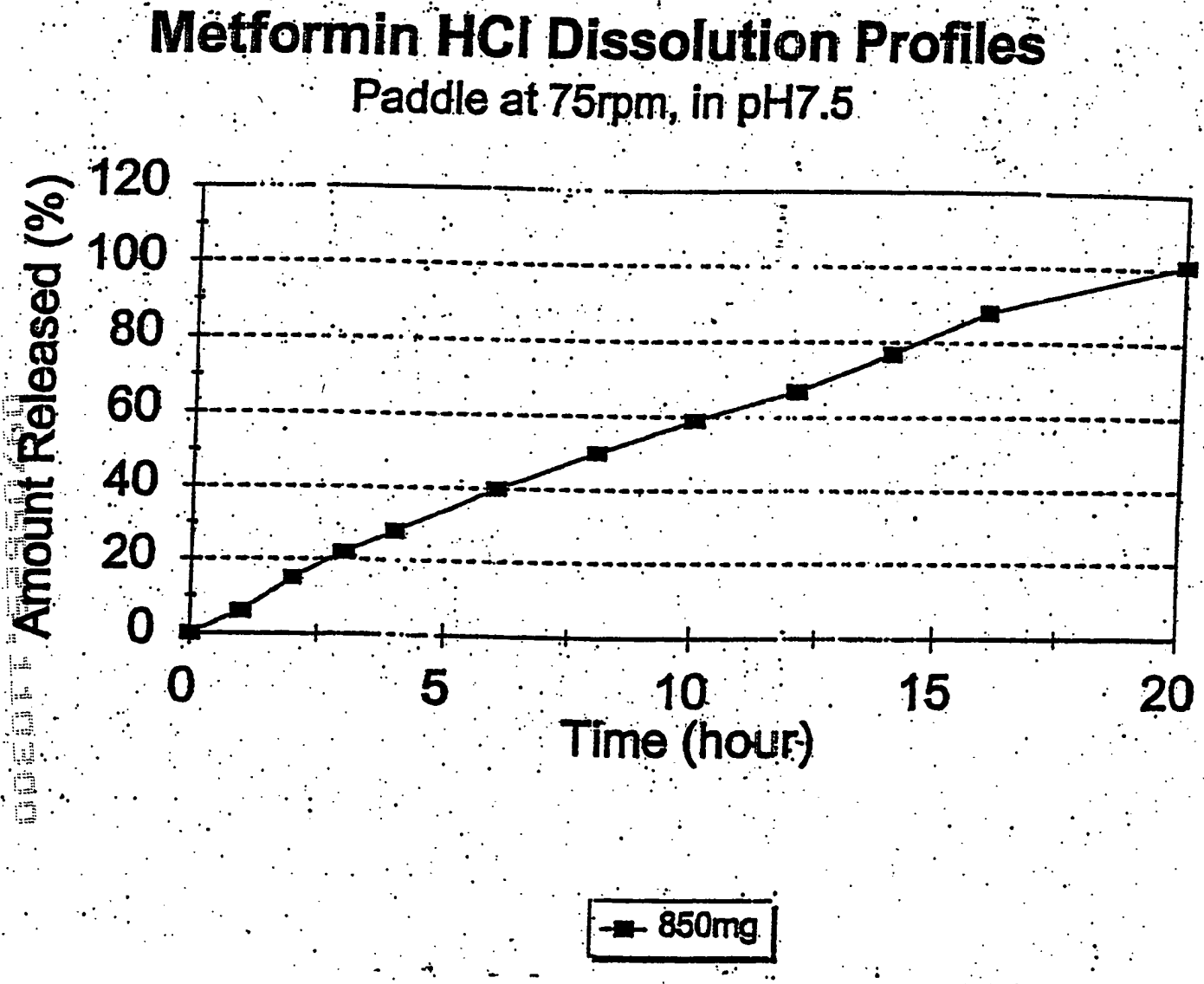

Metformin HCl Dissolution Profiles
Paddle at 75rpm, in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
850mg

FIGURE 7

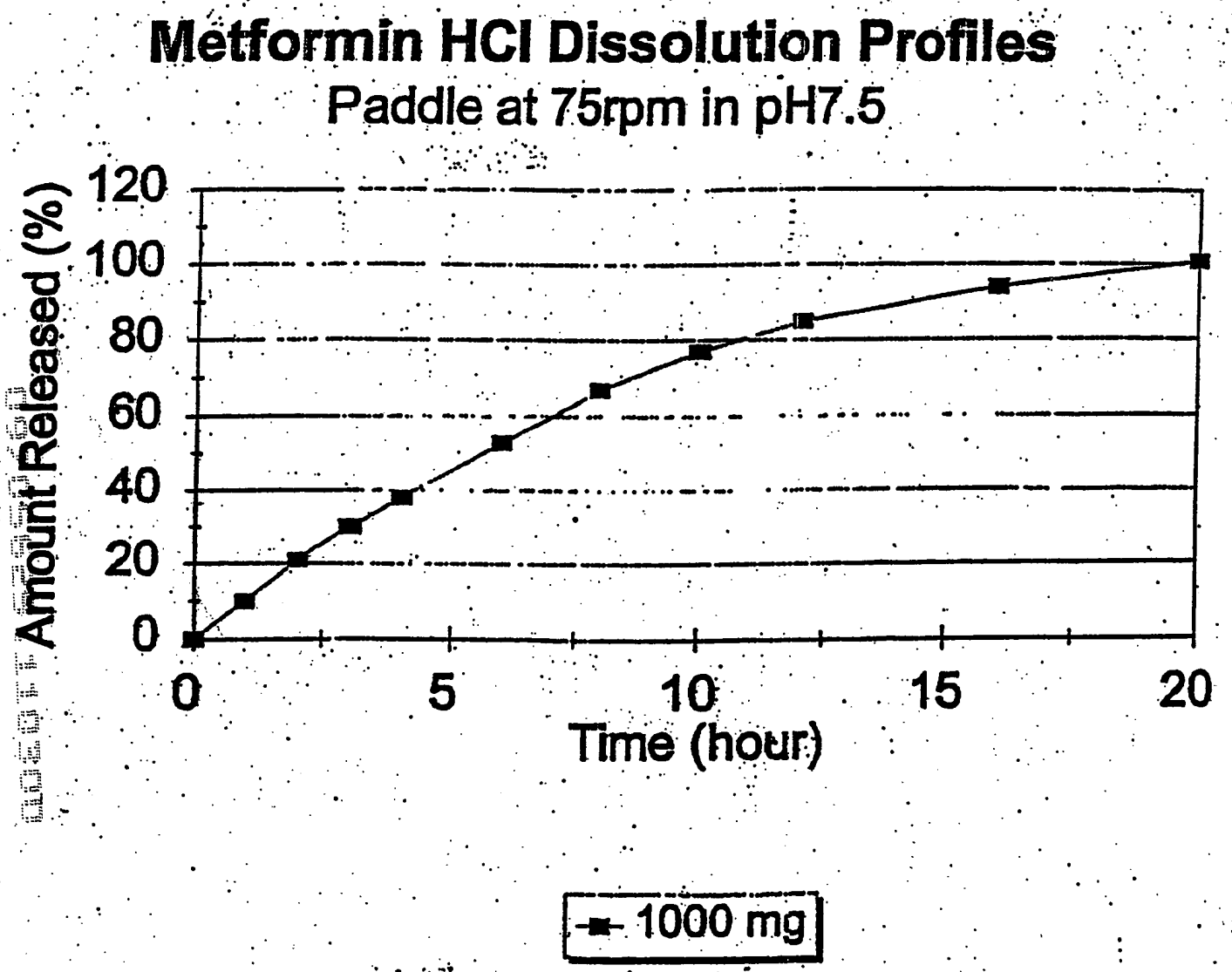

Metformin HCl Dissolution Profiles
Paddle at 75rpm in pH7.5
Amount Released (%)
120
100
80
60
40
20
0
0
5
10
15
20
Time (hour)
1000 mg

FIGURE 8

METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN

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

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

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:

(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

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

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

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

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.

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.

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.

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.

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

(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.

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

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.

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

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%

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

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.

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.

(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).

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.

(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).

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.

(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).

(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.

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:

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

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:

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.

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

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).

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.

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.

WHAT IS CLAIMED IS:

1. A method for 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 at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration.

2. The controlled release dosage form of claim 1 wherein said at least one antihyperglycemic agent 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 method of claim 3, in which the administration of the at least one metformin dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after administration.

5. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at dinner time and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 5.5 to 7.0 hours after the administration.

6. The method of claim 3, in which the administration of the at least one metformin dosage form occurs at breakfast and provides a mean time to maximum plasma concentration (T_{max}) of metformin at from about 6.0 to about 7.5 hours after the administration.

7. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

8. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

9. The method of claim 3, in which the administration of the at east one metformin dosage form 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 administration.

10. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

11. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

12. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

13. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

14. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} from at least 80% of the mean AUC_{0-24} 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.

15. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24hr} that is from at least 90% of the mean AUC_{0-24} 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.

16. The method of claim 3, in which the once-a-day dose of the metformin is administered at dinner.

17. The method of claim 16, in which the once-a-day dose of metformin is administered at fed state.

18. The method of claim 16, in which the once-a-day dose of the metformin is about 2000 mg, which is provided by two controlled release dosage forms containing about 1000 mg metformin each.

19. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

20. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

21. The method of claim 3, in which the administration of the at least one metformin dosage form 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.

22. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

23. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

24. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

25. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma concentration-time profile of metformin substantially as set

forth in FIG. 6, based on administration of a 2000 mg once-a-day dose of metformin at breakfast.

26. The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean plasma glucose concentration-time profile substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

27. The method of claim 3, further comprising administering to said human patients at least one additional pharmaceutically active ingredient for treatment of NIDDM.

28. The method of claim 3, further comprising administering to said human patients an additional pharmaceutically active ingredient for treatment of NIDDM, said additional pharmaceutically active ingredient selected from the group consisting of a sulfonylurea, a glitazone or a second biguanide.

29. The method of claim 3, in which the dose of metformin comprises metformin hydrochloride.

30. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 1000 mg to about 2500 mg.

31. The method of claim 29, in which the once-a-day dose of metformin hydrochloride is about 2000 mg to about 2500 mg metformin.

32. A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering 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 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.

33. The method of claim 32 wherein said dosage form maintains bioavailability from at least 80% of the immediate release composition.

34. The method of claim 32 wherein said dosage form maintains bioavailability from aat least 90% of the immediate release composition.

ABSTRACT

A method 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 a 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.

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2000

Application or Docket Number

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	34	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	34 minus 20=	*
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	355.00	OR	BASIC FEE	710.00
X$ 9=		OR	X$18=	252
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL		OR	TOTAL	962

CLAIMS AS AMENDED - PART II

AMENDMENT A

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

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

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

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.