



[54] ORAL DOSAGE FORM FOR THE CONTROLLED RELEASE OF A BIGUANIDE AND SULFONYLUREA

[75] Inventors: Chih-Ming Chen; Xiu Xiu Cheng, both of Davie; Joseph Chou; Steve Jan, both of Coral Springs, all of Fla.

[73] Assignee: ANDRX Corporation, Fort Lauderdale, Fla.

- 4,863,724 9/1989 Schepky et al.
4,865,598 9/1989 Eckenhoff .
4,871,549 10/1989 Ueda et al. .
4,892,739 1/1990 Shah et al. .
4,963,141 10/1990 Eckenhoff .
5,024,843 6/1991 Kuczynski et al. .
5,030,452 7/1991 Curatolo .
5,071,607 12/1991 Ayer et al. .
5,082,668 1/1992 Wong et al. .

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

- [21] Appl. No.: 09/143,876
[22] Filed: Aug. 31, 1998
[51] Int. Cl.7 A61K 9/24; A61K 9/36; A61K 9/20
[52] U.S. Cl. 424/473; 424/468; 424/474; 424/475; 424/479; 424/480
[58] Field of Search 424/464, 468, 424/472, 473, 474, 475, 479, 480; 604/890.1, 892.1

- 0283369 8/1993 European Pat. Off. .
2320735 8/1975 France .
1522179 11/1976 United Kingdom .
9608243 3/1996 WIPO .
9609823 4/1996 WIPO .
97017975 5/1997 WIPO .
9810786 3/1998 WIPO .
9827982 7/1998 WIPO .
99/03477 1/1999 WIPO .

OTHER PUBLICATIONS

[56] References Cited

U.S. PATENT DOCUMENTS

- 3,845,770 11/1974 Theeuwes et al. .
3,916,899 11/1975 Theeuwes et al. .
3,952,741 4/1976 Baker .
3,957,853 5/1976 Bohoun .
4,034,758 7/1977 Theeuwes .
4,077,407 3/1978 Theeuwes et al. .
4,080,472 3/1978 Bohoun .
4,522,625 6/1985 Edgren .
4,587,117 5/1986 Edgren et al. .
4,609,374 9/1986 Ayer .
4,612,008 9/1986 Wong et al. .
4,615,698 10/1986 Guittard et al. .
4,624,847 11/1986 Ayer et al. .
4,627,850 12/1986 Deters et al. .
4,692,336 9/1987 Eckenhoff et al. .
4,696,815 9/1987 Schepky et al. .
4,704,118 11/1987 Eckenhoff .
4,708,868 11/1987 Brickl et al. .
4,777,049 10/1988 Magruder et al. .
4,803,076 2/1989 Ranade .
4,849,227 7/1989 Cho .
4,851,229 7/1989 Magruder et al. .

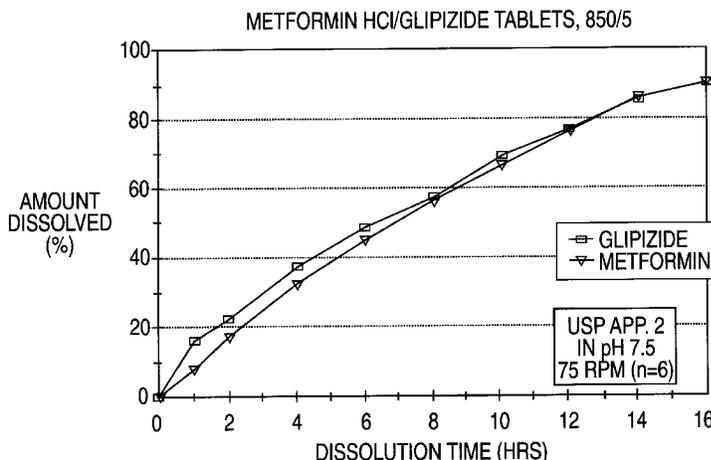
Diem, Drug Therapy of Type-II Diabetes: Tablets, Insulin or a Combination of These, Schweizerische Rundschau Fur Medizin Praxis, 83(2) pp68-71, Jan. 18, 1994. Clin. Ther. 1996 May; 18 (3) : pp. 360-371. By Briscoe TA, et al.; Dept. of Medicine Morehouse School of Medicine; Atlanta, GA. Ann. Intern Med. 1998 Feb. 1; 128 (3) pp. 165-175. Physician's Desk Reference 52th Edition pp. 795-800; 1217-1219; and 2182-2186.

Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Hedman, Gibson & Costigan, P.C.

[57] ABSTRACT

A controlled release pharmaceutical tablet containing anti-hyperglycemic drug and a hypoglycemic drug that does not contain an expanding or gelling polymer layer and comprising a core containing the antihyperglycemic drug and the hypoglycemic drug, a semipermeable coating membrane surrounding the core and at least one passageway in the membrane to allow the drugs to be released from the core.

4 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

5,091,190	2/1992	Kuczynski et al. .	5,543,156	8/1996	Roorda et al. .
5,108,756	4/1992	Curatolo .	5,545,413	8/1996	Kuczynski et al. .
5,110,597	5/1992	Wong et al. .	5,591,454	1/1997	Kuczynski et al. .
5,120,548	6/1992	McClelland et al. .	5,614,578	3/1997	Dong et al. .
5,141,752	8/1992	Ayer et al. .	5,629,319	5/1997	Luo et al. .
5,178,867	1/1993	Guittard et al. .	5,631,224	5/1997	Efendic et al. .
5,185,158	2/1993	Ayer et al. .	5,650,170	7/1997	Wright et al. .
5,260,275	11/1993	Cooper et al. .	5,667,804	9/1997	Wong et al. .
5,308,348	5/1994	Balaban et al. .	5,668,117	9/1997	Shapiro .
5,356,913	10/1994	Colca .	5,674,900	10/1997	Ubillas et al. .
5,413,572	5/1995	Wong et al. .	5,688,518	11/1997	Ayer et al. .
5,512,293	4/1996	Landrau et al. .	5,691,386	11/1997	Inman et al. .

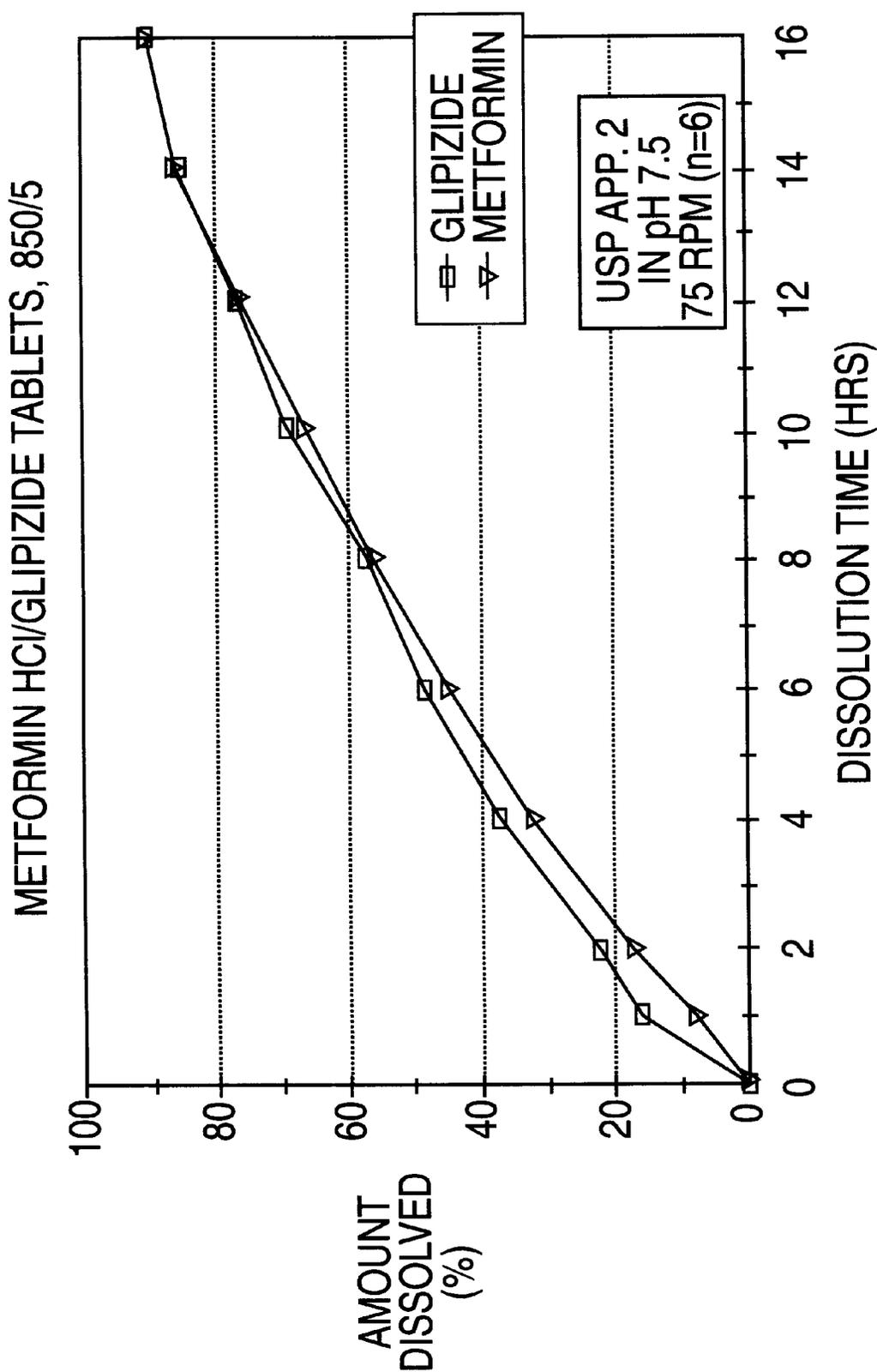


FIG. 1

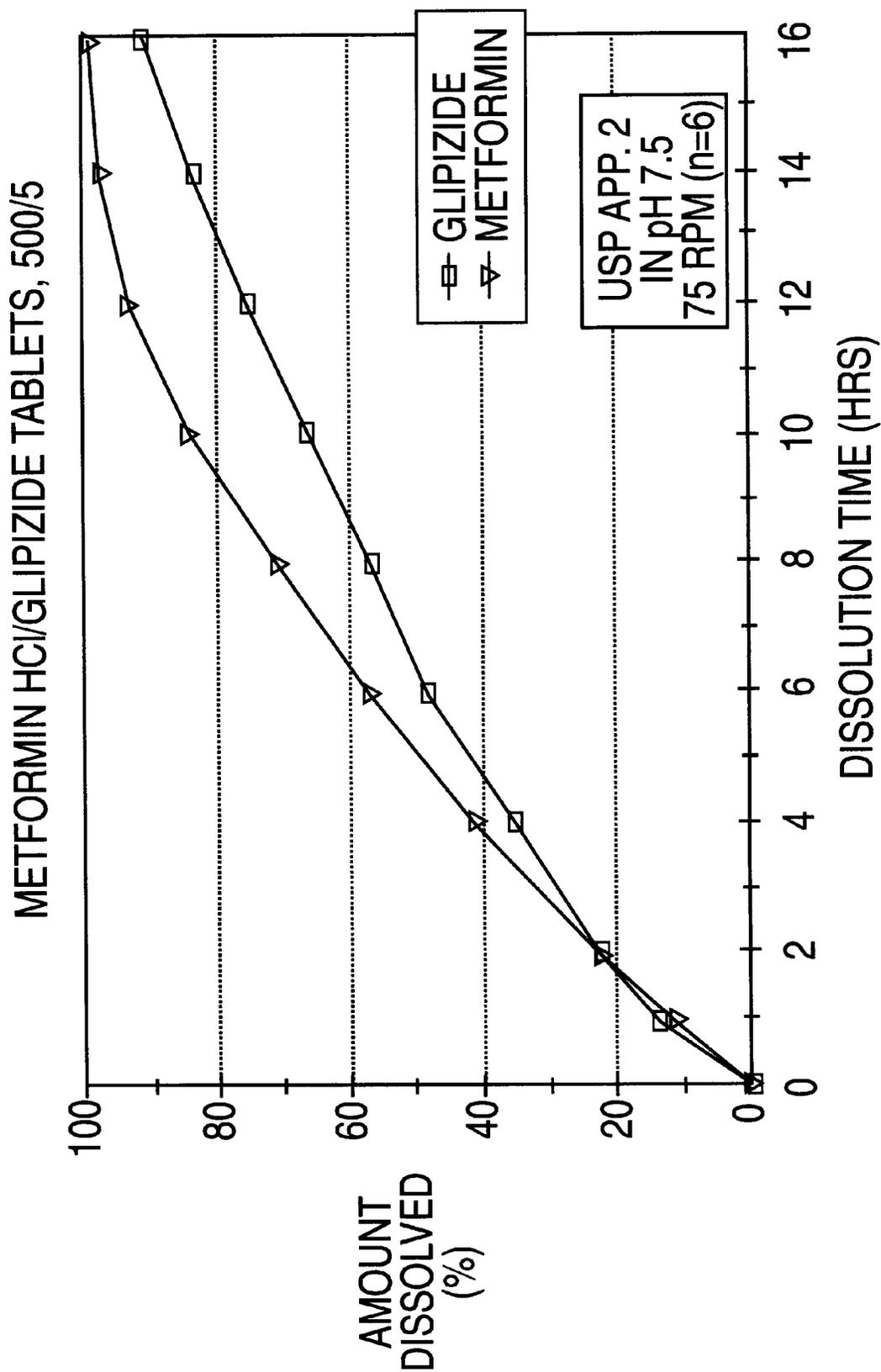


FIG. 2

**ORAL DOSAGE FORM FOR THE
CONTROLLED RELEASE OF A BIGUANIDE
AND SULFONYLUREA**

BACKGROUND OF THE INVENTION

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug and a hypoglycemic drug. As used in this specification the term "antihyperglycemic" refers to a drug that is useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and/or improving insulin sensitivity. Biguanides are the preferred antihyperglycemic drugs. As used in this specification the term "hypoglycemic" refers to a drug that is useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM) by stimulating the release of insulin from the pancreas. Sulfonylureas are the preferred hypoglycemic drugs.

In a preferred embodiment, the present invention relates to an oral dosage form comprising a unique combination of a biguanide and a sulfonylurea. The biguanide is preferably metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference. The sulfonylurea compound is preferably glipizide as described in U.S. Pat. No. 5,545,413 or glyburide. Other possible sulfonylurea compounds such as glibornuride, glisoxepide, gliclazide acetohexamide, chlorpropamide, tolazamide, tolbutamide and tolbutamide which are described in U.S. Pat. Nos. 5,674,900 and 4,708,868, which are incorporated herein by reference, may also be employed.

The dosage form of the present invention can provide therapeutic levels of the drugs from twelve to twenty-four hour periods. In a preferred embodiment, the dosage form will be administered once a day and provide therapeutic levels of the drug throughout the day.

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 employ either a biguanide drug alone or a sulfonylurea drug alone. For example WO 96/08243 discloses a controlled release dosage form containing only metformin HCl, a biguanide, as the active ingredient and employs a hydrogel to push the active ingredient from the dosage form. Similarly, U.S. Pat. Nos. 5,545,413, 5,591,454 and 5,091,190 disclose controlled release dosage forms containing only the drug glipizide and employ a hydrogel to push the active ingredient from the dosage form.

The 50th edition of the Physicians' Desk Reference®, copyright 1996, suggests administering to a patient a metformin HCl dosage form commercially available from Bristol-Myers Squibb Co. under the tradename GLUCOPHAGE® and a dosage form of a sulfonylurea compound such as glyburide. More specifically, page 753 of the 50th edition of the Physicians' Desk Reference states that if adequate glycemic control is not attained with GLUCOPHAGE® monotherapy, the combination of GLUCOPHAGE® and a sulfonylurea such as glyburide may have a synergistic effect, since both active ingredients act to improve glucose tolerance by different mechanism. According to the 50th edition of the Physicians' Desk Reference, the GLUCOPHAGE®

dosage form is believed to function by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity, while the sulfonylurea compound is believed to lower the blood glucose levels by stimulating the release of insulin from the pancreas.

Although the 50th edition of the Physicians' Desk Reference suggests the combined administration of metformin HCl and a sulfonylurea compound, it fails to suggest a single unitary controlled release dosage form comprising both an antihyperglycemic drug and a hypoglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug and a hypoglycemic drug to an animal in need of such treatment over a twelve hour or twenty-four hour period.

It is an object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug.

It is a further object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug that does not employ an expanding or gel forming material to push the drugs out.

It is a further object of the present invention to provide a controlled or sustained release formulation that contains both an antihyperglycemic drug and a hypoglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug to an animal in need of such treatment over a twelve hour or twenty-four hour period.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having a homogeneous core wherein the 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 which comprises:

- (a) a core which comprises:
 - (i) an antihyperglycemic drug;
 - (ii) a hypoglycemic drug;
 - (iii) a binding agent; and
 - (iv) optionally, an absorption enhancer;
- (b) optionally a seal coating layer around the core;
- (c) a semipermeable coating membrane surrounding the core; and
- (d) at least one passageway in the semipermeable membrane to allow release of the antihyperglycemic drug and the hypoglycemic drug.

In the preferred embodiment the antihyperglycemic drug is a biguanide such as metformin or a pharmaceutically acceptable salt and the hypoglycemic drug is a sulfonylurea, such as glipizide or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid (SIF), pH 7.5 phosphate buffer 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 (SIF), pH 7.5 phosphate buffer of the formulation described in Example 2 as tested according

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.