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

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[58] **Field of Search** 424/464, 468, 424/472, 473, 474, 475, 479, 480; 604/890.1, 892.1

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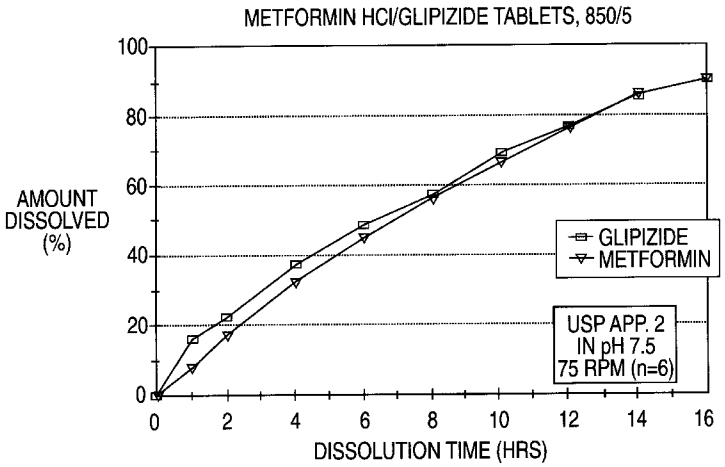
[57] **ABSTRACT**

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



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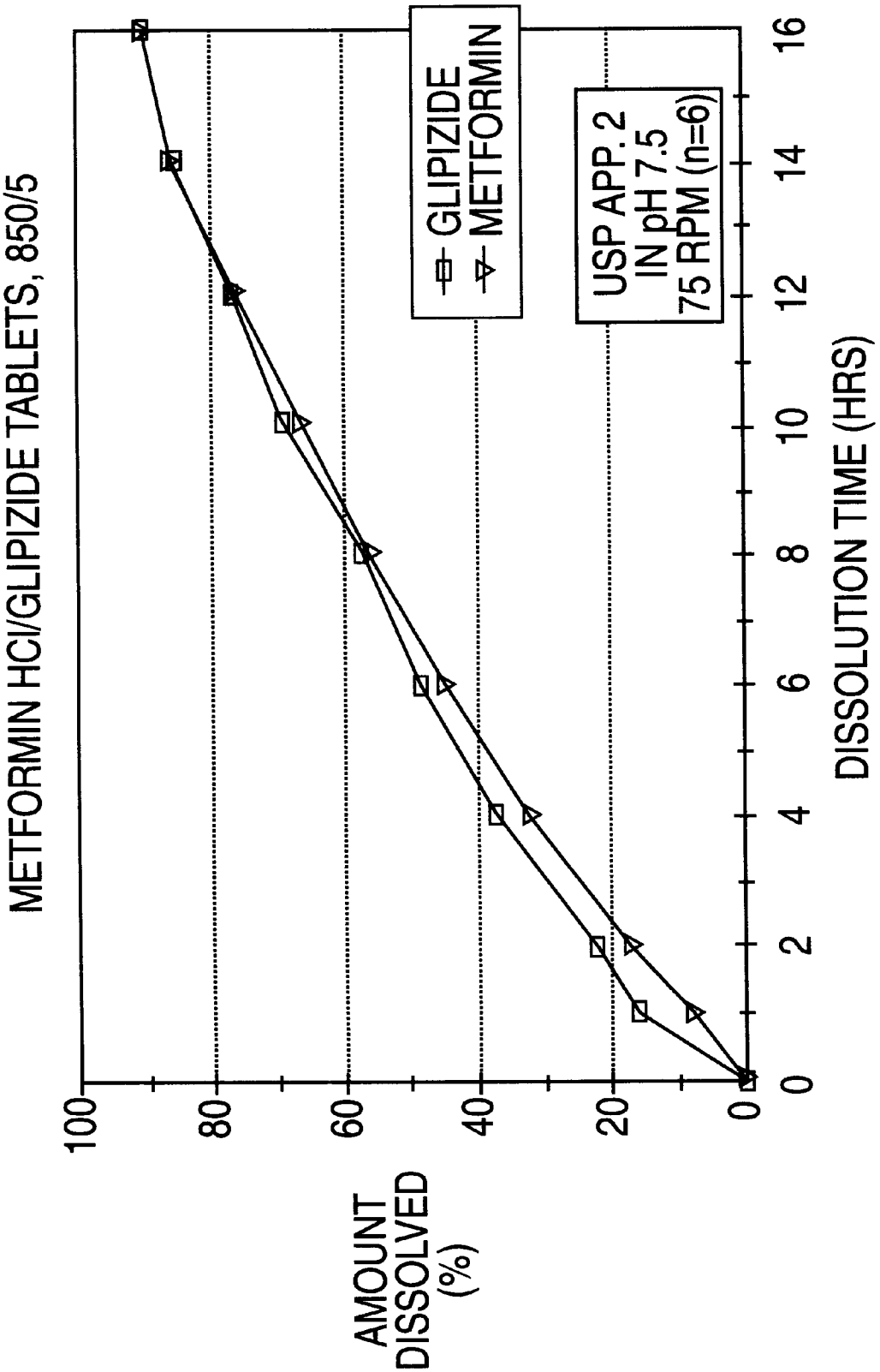

FIG. 1

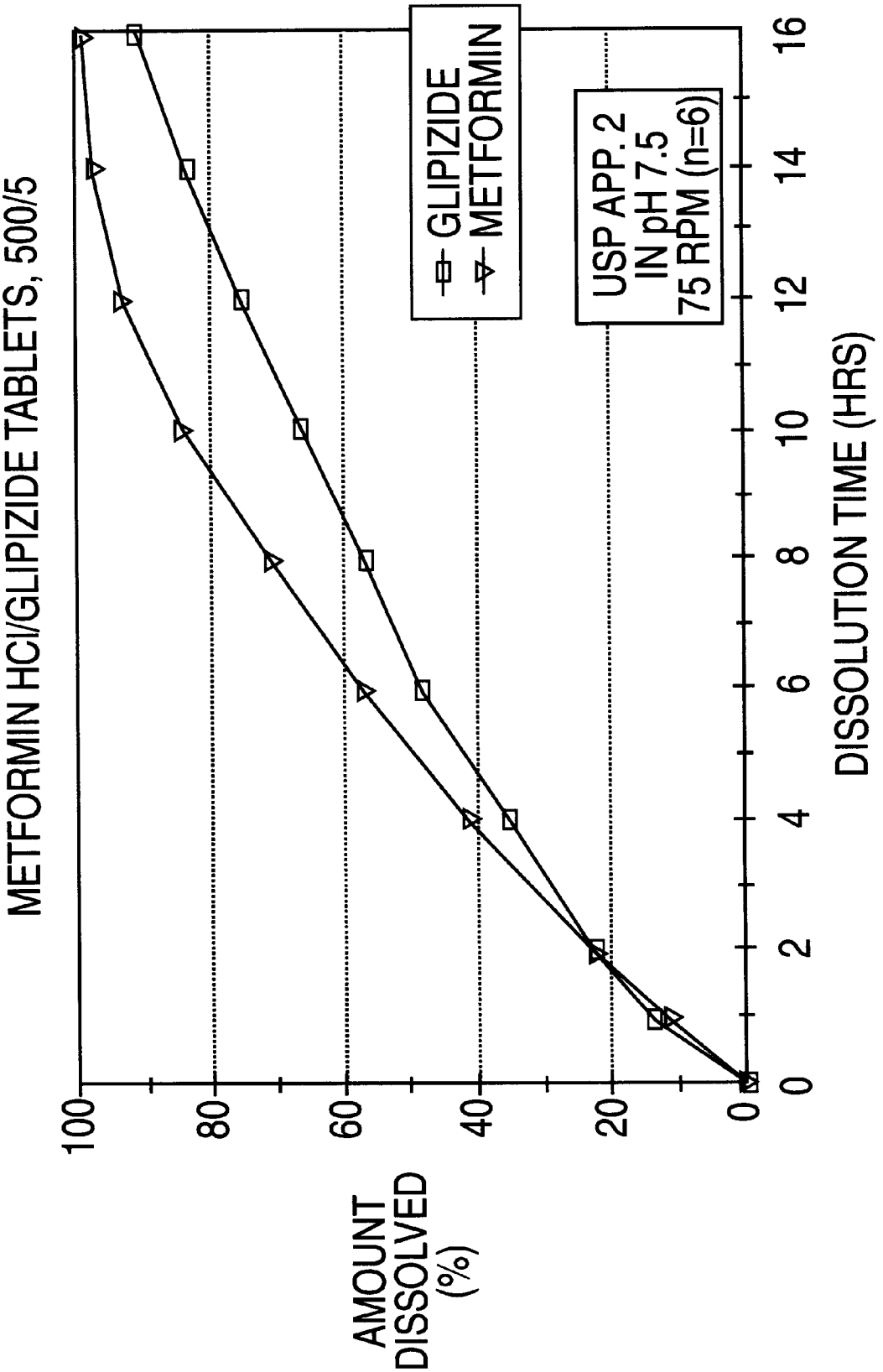

FIG. 2

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 meet 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

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