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**Cheng et al.**

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(54) **METHODS FOR TREATING DIABETES VIA ADMINISTRATION OF CONTROLLED RELEASE METFORMIN**

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A61K 9/20; A61K 9/22; A61K 9/27

(52) **U.S. Cl.** ..... **424/468**; 424/464; 424/465;  
424/469; 424/470; 424/472; 424/474; 424/489;  
424/490

(58) **Field of Search** ..... 424/473, 469,  
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588, 591, 592, 593

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,845,770 A	*	11/1974	Theeuwes et al. ....	424/427
3,916,899 A		11/1975	Theeuwes et al. ....	424/424
3,952,741 A		4/1976	Baker .....	424/405
3,957,853 A		5/1976	Bohuon .....	560/143
4,008,719 A		2/1977	Theeuwes et al. ....	424/427
4,034,758 A		7/1977	Theeuwes .....	424/427
4,036,228 A		7/1977	Theeuwes .....	424/473
4,063,064 A		12/1977	Saunders et al. ....	219/121.7
4,077,407 A		3/1978	Theeuwes et al. ....	424/427
4,080,472 A		3/1978	Bohuon .....	514/555
4,088,864 A		5/1978	Theeuwes et al. ....	219/121.71
4,111,201 A		9/1978	Theeuwes .....	424/473
4,522,625 A		6/1985	Edgren .....	424/473
4,587,117 A		5/1986	Edgren et al. ....	424/473
4,609,374 A		9/1986	Ayer .....	424/473

(List continued on next page.)

**FOREIGN PATENT DOCUMENTS**

WO	9608243	3/1996	.....	A61K/31/155
WO	9929314	6/1999	.....	A61K/31/155
WO	99/47125	*	9/1999	
WO	9947125		9/1999	..... A61K/9/20
WO	9947125 A1	*	9/1999	..... A61K/9/20
WO	9947128		9/1999	..... A61K/9/24
WO	00/28989	*	5/2000	
WO	0028989 A1	*	5/2000	..... A61K/31/353

**OTHER PUBLICATIONS**

Chiao, C. Sustained-Release Drug Delivery Systems Remington: the Science and Practice of Pharmacy, 1995, Mack Publishing Company, Easton, PA pp. 1660-1669.\*  
Drug Facts and Comparisons p. 635-642 1999.\*  
*Physicians Desk Reference* (54<sup>th</sup> Ed. 2000), pp. 831-835.  
Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371.  
Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.  
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.  
Kartunen, P., et al., *The Pharmacokinetics of Metformin: A Comparison of the Properties of a Rapid-Release and a Sustained-Release Preparation*, pp. 31-36.

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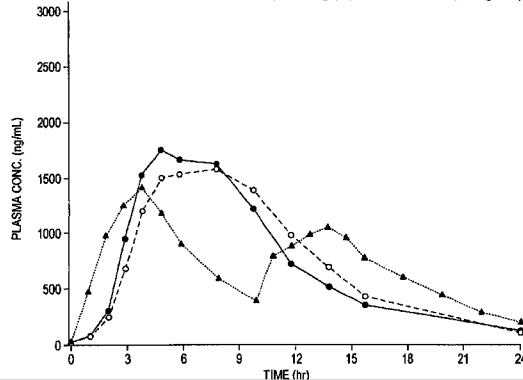
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(57) **ABSTRACT**

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.

**21 Claims, 8 Drawing Sheets**

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.)



U.S. PATENT DOCUMENTS

4,612,008 A	9/1986	Wong et al. ....	604/892.1	5,512,293 A	4/1996	Landrau et al. ....	424/449
4,615,698 A	10/1986	Guittard et al. ....	604/892.1	5,543,156 A	8/1996	Roorda et al. ....	424/484
4,624,847 A	11/1986	Ayer et al. ....	424/467	5,545,413 A	8/1996	Kuczynski et al. ....	424/473
4,627,850 A	12/1986	Deters et al. ....	604/892.1	5,591,454 A	1/1997	Kuczynski et al. ....	424/486
4,692,336 A	9/1987	Eckenhoff et al. ....	424/468	5,614,578 A	3/1997	Dong et al. ....	524/377
4,704,118 A	11/1987	Eckenhoff .....	424/438	5,629,319 A	5/1997	Luo et al. ....	514/284
4,777,049 A	10/1988	Magruder et al. ....	424/457	5,631,224 A	5/1997	Efendic et al. ....	514/12
4,783,337 A	11/1988	Wong et al. ....	424/468	5,650,170 A	7/1997	Wright et al. ....	424/473
4,851,229 A	7/1989	Magruder et al. ....	424/457	5,667,804 A	9/1997	Wong et al. ....	424/472
4,865,598 A	9/1989	Eckenhoff .....	604/892.1	5,668,117 A	9/1997	Shapiro .....	514/55
4,892,739 A	1/1990	Shah et al. ....	424/473	5,674,900 A	10/1997	Ubillas et al. ....	514/557
4,963,141 A	10/1990	Eckenhoff .....	604/892.1	5,688,518 A	11/1997	Ayer et al. ....	424/422
5,024,843 A	6/1991	Kuczynski et al. ....	514/255.06	5,691,386 A	11/1997	Inman et al. ....	514/691
5,071,607 A	12/1991	Ayer et al. ....	264/112	5,858,398 A	1/1999	Cho .....	424/450
5,091,190 A	2/1992	Kuczynski et al. ....	424/473	5,955,106 A *	9/1999	Moeckel et al. ....	424/464
5,110,597 A	5/1992	Wong et al. ....	424/438	6,010,718 A	1/2000	Al-Razzak et al. ....	424/464
5,120,548 A	6/1992	McClelland et al. ....	424/473	6,099,859 A *	8/2000	Cheng et al. ....	424/464
5,141,752 A	8/1992	Ayer et al. ....	424/473	6,099,862 A *	8/2000	Chen et al. ....	424/473
5,178,867 A	1/1993	Guittard et al. ....	424/473	6,270,805 B1 *	8/2001	Chen et al. ....	424/497
5,185,158 A	2/1993	Ayer et al. ....	424/473	6,284,275 B1 *	9/2001	Chen et al. ....	424/473
5,308,348 A	5/1994	Balaban et al. ....	604/892.1	6,475,521 B1	11/2002	Timmins et al. ....	424/469
5,413,572 A	5/1995	Wong et al. ....	604/892.1				

\* cited by examiner

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.)

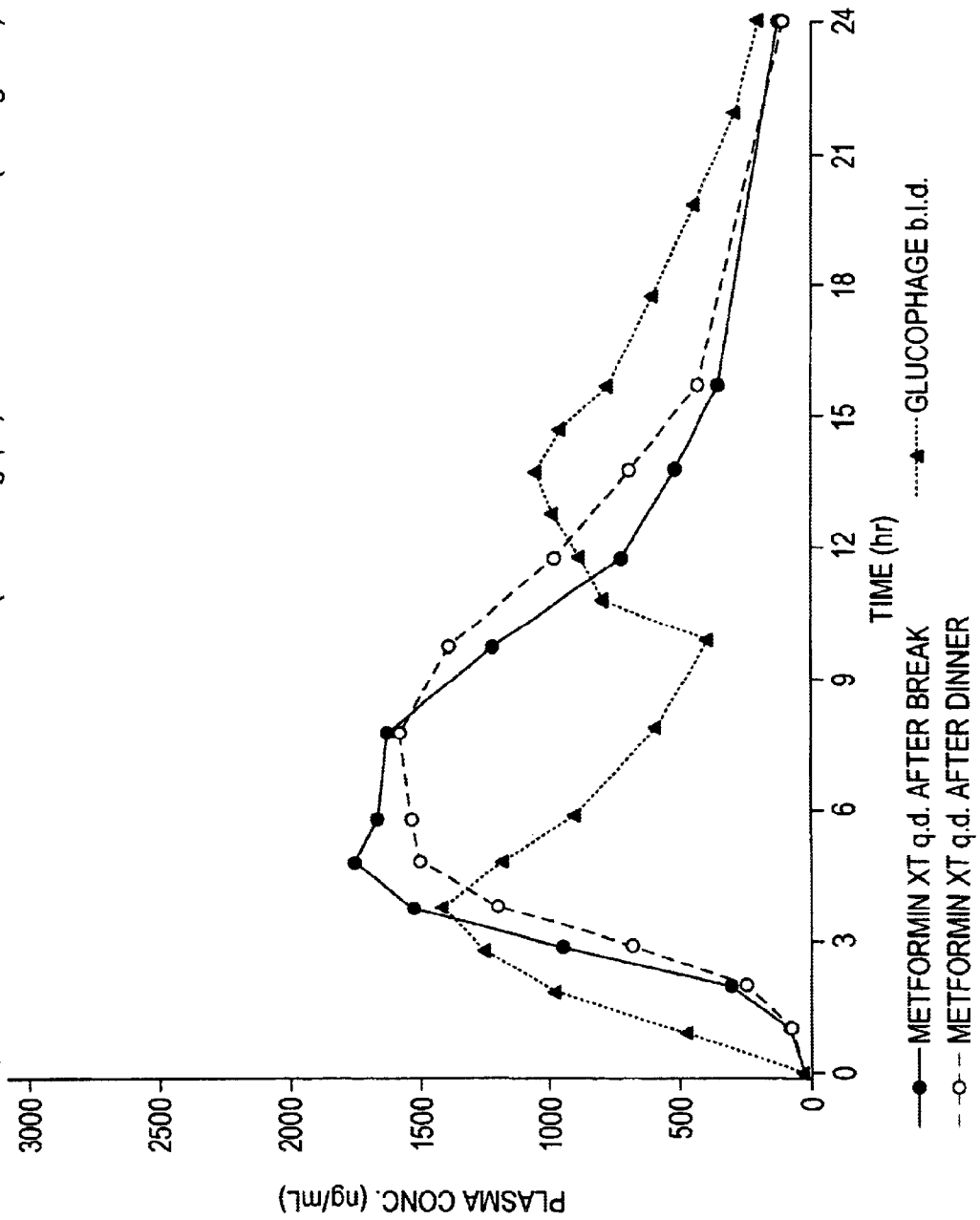


FIG. 1

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN TWELVE SUBJECTS AFTER AN ORAL ADMINISTRATION OF METFORMIN XT (4 x 500 mg q.d.) OR GLUCOPHAGE (2 x 500 mg b.i.d.)

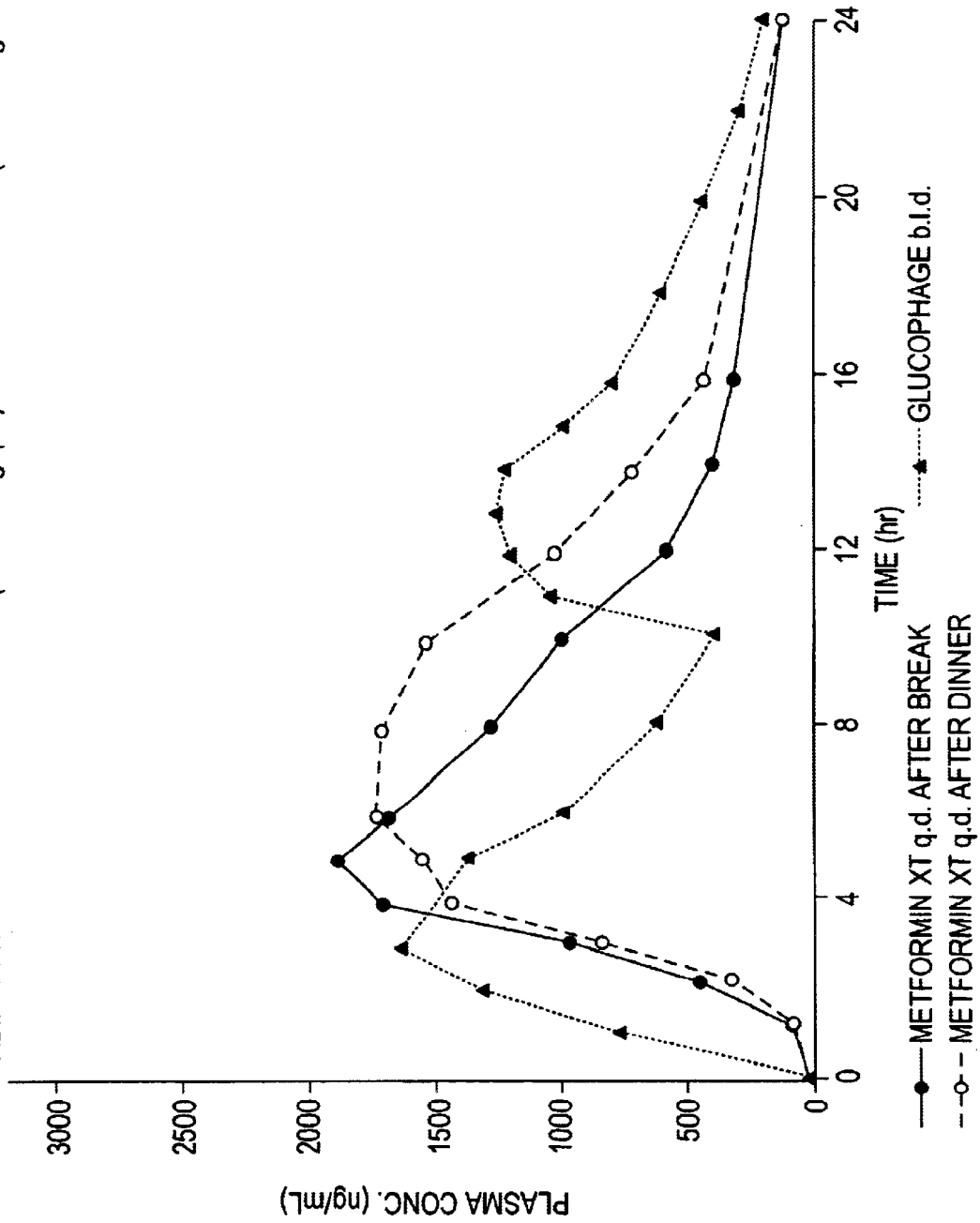


FIG. 2

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

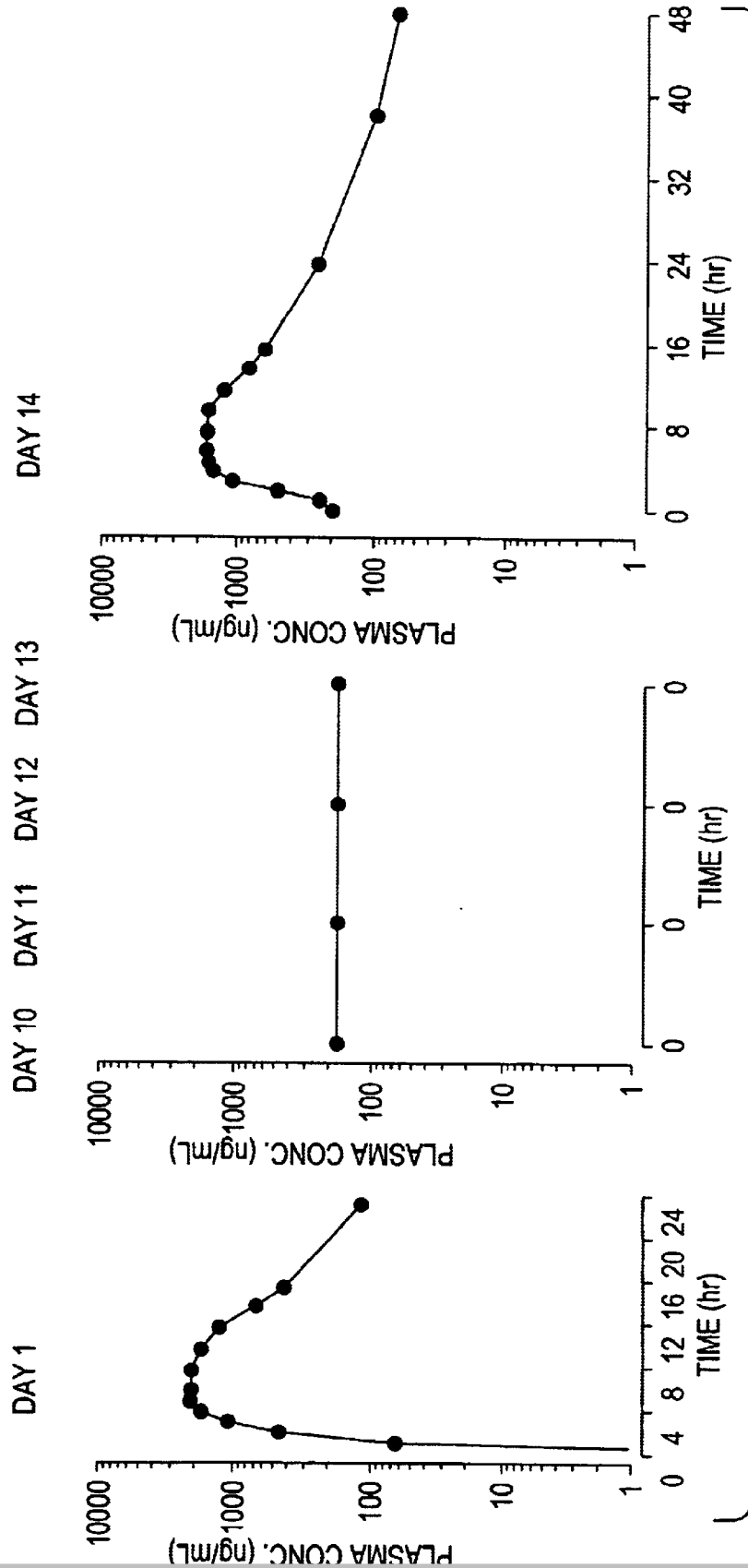


FIG. 3

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