CHAPTER 1.

INTRODUCTION
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The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and is expected to increase to 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people ≥ 65 years of age. (Wild et. al., 2004)

Socioeconomic environment influences occupation, lifestyle, and nutrition of social classes which in turn would influence the prevalence and profile of glucose intolerance and diabetic complications. A number of studies have addressed this issue in western countries. (Kelly et. al. 1993; Unwin et al., 1995; Evans, 2000)

In urban India, there are wide social and economic disparities. Free health care facilities are available for the economically backward classes, but due to the low level of education and occupational problems, the facilities are not always used. The expenditure increases if the patients are hospitalized and further rise will be incurred if they need any surgery. Patients with diabetic complication such as foot complications or kidney complication require additional and continuing expenses for specialized care. (Ramachandran et. al., 2003).

It was estimated that an average of Rs. 4,500 was spent for each patient per year, either by the patient himself or by the institution. (Shobhana et. al., 2000). A recent analysis has shown a further increase in the expenditure to an average of Rs.10,000/- per annum in the urban areas and Rs.6,260/- per annum in the rural areas (Ramachandran et al., 2007 suppl.).

Considering a rather low estimate of approximately 20 million diabetic patients in India, the annual estimated cost could be Rs.90,200/- million (U.S. $ 2.2 billion) for diabetes
health care. The ADA reported that direct cost of diabetes health care in USA was US $ 45.2 billion in 1993. The difference between the two estimates highlights the large differences in medical care expenditure between developing and developed countries. While studying the cost of diabetes health care it is important to take into account only the expenditure directly related to diabetes. (Ramachandran et. al., 2007)

Asian Indians are genetically predisposed to insulin resistance (Singh et al. 1995) and because of this, in conjunction with a more sedentary lifestyle, higher total and saturated fat consumption and a higher intake of cholesterol and refined carbohydrates, they are at a high risk of developing type 2 diabetes (Ramachandran et al., 1999)

Metformin, a biguanide oral antihyperglycemic, is well established as a first line therapeutic agent in patients with type 2 diabetes mellitus. It has a unique mechanism of action, proven efficacy, and a favorable safety profile. Metformin produces clinically significant improvements in glycemic control in patients with type 2 diabetes through its insulin-sensitizing actions on both the liver, where it reduces hepatic glucose overproduction, and peripheral tissues (particularly skeletal muscle), where it enhances glucose uptake (Glucophage XR US Prescribing Information, 2006).

Metformin typically reduces basal and postprandial hyperglycemia by >25% in >90% of patients when given alone or with other therapies during a program of managed care (Howlett HC et. al, 1999.). In the U.K. Prospective Diabetes Study, intensive glucose control with metformin appeared to reduce the risk of diabetes-related end points in overweight patients and was associated with less weight gain and fewer hypoglycemic attacks than insulin (UK Prospective Diabetes Study (UKPDS) Group, 1998)

Metformin hydrochloride is available worldwide in a number of countries in solid dosage form (immediate release and extended release tablets) and as oral solution (New Product Focus, 2004, IMS Health Incorporated).

Non-compliance with the pharmacological therapy in patients with type 2 diabetes can have serious short-term and long-term adverse effects. Short-term consequences include precipitation of diabetic ketoacidosis, a condition that can be life threatening.
Long-term consequences of non-compliance include macrovascular, neurologic and microvascular complications: retinopathy, nephropathy, neuropathy, and cardiovascular disease. These complications cause major morbidity and mortality in diabetic patients. Indeed, intensive control of blood glucose in type 2 diabetics has been shown to reduce the progression of microvascular disease as well as cardiovascular disease (UK Prospective Diabetes Study Group, 1998).

An extended release formulation of metformin 500 mg is marketed in the USA (Metformin XR of Bristol Myers Squibb), and a 750 mg extended release formulation of the same manufacturer has been approved for the same manufacturer in the USA (Timmins et al., 2005). Metformin XR has been shown to produce systemic metformin exposures similar to those of IR and to be therapeutically as effective and as well tolerated on once daily dosing as equal daily doses of IR metformin given in divided doses.

In India the multiplicities of available formulations in the generic and branded generics arena assist in reducing costs of drug therapy. Indian markets are flooded with a huge number of branded formulations, available for every drug molecule, with significant pricing difference between the different brands of the same formulation. This apart from creating confusion among innocent consumers, often, allows them to be misled by unfair traders. Price difference between different brands of products (single drug or drug combinations) were found to vary up to the extent of 7% to 881% (Das, 2007).

A number of sustained release preparations of the drug are commercially available on the Indian market. These slow release products are formulated in various ways that decrease the rate of disintegration and dissolution of the drug, thus affecting the bioavailability. The medical profession has realized the problem of wide variations in the therapeutic effectiveness of various brands of oral formulations containing the same active ingredient in equal amounts. Determination of CI is a current regulatory requirement of DCGI (Drug Controller General of India) and also of FDA (CDER, 2003) to document bioequivalence. However, Most of the bioequivalence studies on which the claims of bioequivalence to innovator product do not use confidence intervals (CI) (Parvez et al., 2004).

Only a few published studies are available to document the Bioequivalence of modified release metformin formulations in the fed state (Pervez et al., 2004). Hence, the objective of the proposed study is to compare the pharmacokinetic bioequivalence of two marketed
brands of Metformin sustained release tablets 500 mg with the comparator formulation after a single dosing in healthy, adult, male human subjects under fed conditions.