Introduction
Diabetes mellitus is a heterogeneous disease characterized by an absolute (type I) or relative (type II) deficiency of insulin and insulin resistance. Clinical manifestations include hyperglycemia, glycosuria, altered protein, fat and carbohydrate metabolism and chronic complications resulting from macro and microvascular pathology (DeFronzo, 1988). Insulin resistance has emerged as an important pathogenic factor in both type I and type II diabetes. Chronic lack of insulin, the primary pathogenic abnormality in type I diabetic patients may lead to development of insulin resistance. Various studies have also reported that most insulin-dependent (IDDM or type I) diabetic patients may be moderately to severely resistant to the actions of insulin both at onset and after long duration of diabetes (Walker et al., 1963; Alford et al., 1971). Non-insulin-dependent diabetes (NIDDM or type II) is also an insulin resistant state, although insulin response may be in the normal range or lower (Alford et al., 1971; Beck-Nielsen et al., 1980; Bonora et al., 1989).

Insulin resistance can be due to various causes (Olefsky & Molina, 1990). Since the primary cellular lesions responsible for insulin resistance and abnormal β-cell function are unresolved, the identity of the most fundamental therapeutic targets remains elusive. Also, the multiplicity of interacting factors that contribute to the etiology and pathogenesis of type I and type II diabetes makes it difficult to select specific early intervention therapies. Blood glucose control has been the key objective in the management of type I and type II diabetes (American Diabetes Association, 1994; Alberti et al., 1994). Achieving and maintaining glucose concentrations as near to normal as possible can prevent, defer and slow the progression of long term microvascular and macrovascular complications, reducing mortality and improving the quality of life (Bailey, 2000).

The traditional anti-diabetic agents that are in use even today are insulin, sulfonylureas and biguanides. Insulin therapy has been life saving for the patients with IDDM. It is still the only effective alternative when oral anti-diabetic drugs can no longer achieve adequate glycemic control in NIDDM patients (Edelman & Henry, 1995). Despite many
formulations and mixtures of human insulin with different durations of action, use of multiple daily injection regimens and programmable mini-pumps do not mimic the normal portal delivery and momentary fluctuations in circulating insulin. The prospect of non-injectable means of insulin delivery has always been attractive but has achieved little success to date. Intensive insulin therapy is constrained by the risk of hypoglycemia (Edelman & Henry, 1995). Moreover, the treatment of hyperglycemia might not be compatible with other components of metabolic syndrome, for example, over-zealous use of insulin, which can produce peripheral hyperinsulinaemia, can increase adiposity and aggravate insulin resistance.

Therapy with sulfonylureas available since the 1950s has been in the mainstay of oral treatment for over 40 yrs. Since defective insulin action is thought to be more important than failure of insulin secretion in the development of NIDDM, this raises doubts about the intrinsic suitability of anti-diabetic treatment that is based entirely upon the stimulation of insulin release. However, sulfonylureas are widely considered as first line drug treatment in NIDDM patients who are not grossly obese. The major disadvantage of sulfonylurea treatment is not only the occurrence of hypoglycemia but also the associated cardiovascular morbidity and mortality (Meinert et al., 1970; Asplund et al., 1983; Berger et al., 1986; Ferner & Neil, 1988). A major problem in the long term treatment of diabetes mellitus is secondary failure of oral hypoglycemic agents i.e. decreased responsiveness to drugs. Number of patients with secondary failures seems to increase with a longer duration of diabetes (Groop et al., 1989a).

Biguanides were introduced for the treatment of NIDDM in the mid-1950s, but were subsequently withdrawn in the US in the early 1970s because of the fetal cases of lactic acidosis, mainly associated with phenformin. However, metformin is still considered to be a first-line drug treatment in the obese NIDDM patients. Metformin appears to decrease the fasting and postprandial hyperglycemia primarily by increasing insulin-dependent suppression of hepatic glucose production (DeFronzo et al., 1991) and increasing peripheral glucose disposal in patients with
clear evidence of insulin resistance (Giugliano et al., 1993) and perhaps by decreasing appetite. The major side effects associated with metformin are gastrointestinal which include anorexia, abdominal discomfort and diarrhoea. It is contraindicated in patients with renal insufficiency and cardiovascular disease due to risk of lactic acidosis.

Acarbose, α-glucosidase inhibitor (Lebovitz, 1998) delays intraluminal production of monosaccharides, particularly glucose, by competitively inhibiting the α-glucosidases that are associated with the brush border membrane of the small intestine that are responsible for the digestion of complex oligosaccharides and sucrose, thereby diminishing post-prandial hyperglycemia (Lebovitz, 1992). However, the principal side effects of this therapy on gastrointestinal tract i.e. flatulence and loose stools followed by abdominal distension, diarrhoea caused by an increase in gas formation due to fermentation of unabsorbed carbohydrates in the bowel have limited their use in diabetic patients (Hollander, 1992)

Since insulin resistance is the pathogenic feature of both type I and type II diabetes and an underlying cause of the accompanying cardiovascular risk profile, drugs designed to combat insulin resistance should logically be the fundamental therapeutic approach. So far biguanides was the only class, however, recently a newer class, thiazolidinediones also known as glitazones has been shown to enhance the sensitivity of muscle and adipose tissue to the action of insulin (Bailey, 2000). They are found to enhance glucose uptake in muscle and adipose tissue, reduce gluconeogenesis and glycogenolysis in the liver. These agents improve sensitivity to insulin by binding to nuclear peroxisome proliferator activated receptors γ (PPAR γ) which acts in conjunction with retinoid x receptor by de-repression to increase transcription of certain insulin sensitive genes (Spiegelman, 1998). Although their therapeutic efficacy has been found to be promising clinically, troglitazone has been withdrawn from the market as result of idiosyncratic hepatotoxicity (Saleh et al., 1999). However, this has not been observed with rosiglitazone or pioglitazone.
The efficacy of current agents is compromised in several ways. Individual oral agents act on only part of the pathogenic process, and only to a partial extent (Bailey & Turner, 1996; Lebovitz, 1998; Day, 1999; DeFronzo, 1999; Howlett & Bailey, 1999; Lebovitz, 1999). They do not reinstate normal insulin sensitivity or normal β-cell function. In addition, these agents do not prevent gradual β-cell loss and their usefulness depends upon a critical mass of functional β-cells remaining. Thus, although existing classes of anti-diabetic agents offer a variety of actions that can be combined in a complementary and additive manner, few patients maintain the recommended targets for the good glycemic control, and a normal physiological pattern of glucose homeostasis is rarely reinstated. This emphasizes the urgent need for newer and better therapeutic approaches. The search for improved anti-diabetic drug therapies must take account of the multiplicity of endocrine and metabolic disturbances and attendant risks and complications of diabetic state.

Though the intricate relationship between nutrition and diabetes mellitus was suspected as early as 1674, the exact pathogenetic role of malnutrition in diabetes mellitus has been disputed. A variety of dietary recommendations made by different diabetologists so far concentrated on regulation of macronutrient intake. However, over last 20 yrs numerous studies have found alterations in micronutrient status of patients with diabetes mellitus. There is now increasing evidence that micronutrient intake may also be important in promoting optimum health of diabetic patients (Mooradian & Morley, 1987).

Altered trace element metabolism in both type I and type II diabetes mellitus has been well established in both human and experimental animals studies [Mooradian & Morley, 1987; Rossetti et al., 1990]. Both deficiencies and excesses of metals have been observed [Mateo, 1978; Failla & Kiser, 1981]. Induced dietary deficiency of some trace elements in experimental animals have resulted in impaired insulin release, glucose intolerance and insulin resistance [Hambidge, 1974; Asayama, 1986; Mooradian & Morley, 1987]. Conversely, supplementation of deficient nutrient has been shown to improve glucose
homeostasis in a number of studies. Few studies have also addressed the possibility of trace element supplementation as an adjunct therapy in human diabetic subjects, with mixed results.

**Vanadium**

Vanadium (V), a group Va transition element, is ubiquitous in nature and is known to exist in several oxidation states. Vanadium has been shown to be essential for normal cell growth and development in some mammalian species including rats and chicks (Cantley & Aisen, 1979; Erdman et al., 1984) and in mammalian cell cultures (Degani et al., 1981). However, the significance of this element in man is still unknown (Nielsen & Sandsteadt, 1984; Nielsen, 1986).

Physiological effects of vanadium were studied long before (in 1876) its current renaissance. In 1899, vanadium salts were reported to reduce glycosuria in diabetic patients. Interest in the use of vanadium derivatives for the treatment of diabetes was rekindled when in 1979, vanadium compounds were shown to increase glucose transport and oxidation in adipocytes (Shechter & Karlish, 1980; Tamura et al., 1984b; Duckworth et al., 1988) and skeletal muscle (Clark et al., 1985), to stimulate glycogen synthesis in liver and diaphragm and to inhibit gluconeogenesis in hepatocytes (Gil et al., 1988; Rodriguez-Gil et al., 1991). These insulin like effects of vanadium were rapidly confirmed and dissociated from its ability to inhibit Na⁺K⁺-ATPase. Since then, vanadium salts have been found to mimic most biological effects of insulin in various cell types.

After the initial discovery by Heyliger et al. (1985) of glucose lowering and cardioprotective effects of sodium orthovanadate orally administered in STZ-diabetic rats, there has been a growing interest in the potential use of vanadium in diabetic therapy. Absorption of orally administered inorganic vanadium from the gastrointestinal tract ranges from 1 to 10% and depends on its chemical nature and solubility (Underwood, 1977; Conklin et al., 1982). Vanadate treatment at the dose required to produce insulin-like effects has been associated with dehydration and diarrhea, which resulted in the death of some animals.
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(Heyliger et al., 1985; Domingo et al., 1991a). Vanadyl which was reported to be less toxic than vanadate (Water, 1977; Harris et al., 1984), was shown to be as effective as vanadate in producing glucose lowering effects of vanadium in diabetic rats (Ramanadham et al., 1989a, 1989b; Pederson et al., 1989; Ramanadham et al., 1990; Sakurai et al., 1990). In an attempt to increase the potency and decrease toxicity it was speculated that an organic matrix that would increase the lipophilicity of vanadium, would increase the gastrointestinal absorption, and thereby would decrease the dose of vanadium required to produce its effects. Several attempts have been made so far choosing ligands that would impart specific features such as improved lipophilicity (Cam et al., 1993a), potentiation of in vitro insulin mimetic effect (Kadota et al., 1987; Shisheva & Shechter, 1993b; Posner et al., 1994), facilitation of transmembranal ion uptake (Shechter et al., 1992).

Bis(maltolato)oxovanadium (IV) (BMOV) (McNeill et al., 1992), prepared by combining maltol and vanadyl sulphate, was specifically designed to be better absorbed across the gastrointestinal membranes. Acute studies indicated that BMOV was 1.5 times as potent as vanadyl sulfate with respect to the glucose lowering effect (Yuen et al., 1993a; Yuen et al., 1995). When administered orally, it was found to effectively normalize food and fluid intakes and plasma levels of glucose and lipids and also to relieve diabetes related changes in STZ-diabetic rats (Dai et al., 1993; Yuen et al., 1993b, Yuen et al., 1999). In a similar attempt a newer vanadyl complex was synthesized in our laboratory.

Hence, the objective of the present investigation was

1. to study the effect of newly synthesized vanadium complex in various experimental models of diabetes mellitus and compare its efficacy with BMOV
2. to investigate its mechanism of action.
Chromium

Chromium, a group VIb transition element, is one of the essential elements required for normal carbohydrate and lipid metabolism [National Research Council, 1989; Anderson, 1993a]. Deficiency of chromium has been implicated as one of the causes of diabetes mellitus. Chromium deficiency is reported to be associated with glucose intolerance, elevated serum glucose, cholesterol, triglyceride levels and decreased high density lipoprotein levels in humans [Mertz, 1993; Anderson, 1995a].

Studies in animals reported that chromium supplementation resulted in at least partial reversal of glucose intolerance (Mertz et al., 1956; Mertz & Schwarz, 1959; Schwarz & Mertz, 1959; Steele & Forbish, 1977; Tuman & Doisy, 1977). However, when these studies were repeated in man, the results obtained were varied. While various well-controlled clinical trials have shown improvement in glucose tolerance (Offenbacher & Pi-Sunyer, 1980; Riales & Albrink, 1981; Mossop, 1983; Saner et al., 1983), others found improvement in 40-60% of the patients evaluated (Glinsmann & Mertz, 1966; Levine et al., 1968; Anderson et al., 1983a), no response (Sherman et al., 1968; Rabinowitz et al., 1983a; Hunt et al., 1985; Offenbacher et al., 1985; Uusitupa et al., 1992; Thomas & Gropper, 1997; Trow et al., 2000) or deterioration of glucose control (Wise, 1978). It has also been observed that subjects with good glucose tolerance who do not need additional chromium do not respond to supplemental chromium (Anderson, 1993a; 1995a). Subjects consuming adequate chromium and well balanced diets also do not respond to additional chromium (Offenbacher et al., 1985). Moreover, most of the investigators reporting beneficial effects with chromium supplementation in clinical (Riales and Albrink, 1981; Urberg & Zemmel, 1987; Anderson et al., 1991b; Anderson et al., 1997a) as well as experimental (Mertz et al., 1961; Striffler et al., 1995; Anderson et al., 1997b) set up found that observed effects of chromium depended upon the existence of a deficiency state. Hence, it is claimed that chromium is a nutrient and not a drug and will therefore benefit only those who are deficient or marginally deficient in chromium (Anderson, 1998).
Thus, although the essentiality of chromium in normal glucose homeostasis has been established, its usefulness as a therapeutic agent for the treatment of diabetes mellitus of variable etiology (other than chromium deficiency) remains questionable.

Hence, the objective of present investigation was

1. to study the effectiveness of chromium compounds as therapeutic agents in various experimental models of diabetes mellitus
2. to investigate into their mechanism of action