PREFACE

This thesis entitled “Therapeutic Management of Diabetes And Its Complications With Novel Targets” comprises of the work done by the author in pharmacology in the Biological research division, Glenmark Research Centre, Mumbai, and Department of Pharmaceutical Technology, Jadavpur University, Kolkata, for the degree of Doctor of Philosophy in Pharmacy.

Diabetes mellitus (DM) is being diagnosed at an alarming rate around the world. More than 90% of the estimated 200 million persons affected with diabetes worldwide have type 2 diabetes. Type 2 diabetes is preceded by a long period of impaired glucose tolerance (IGT), a potentially reversible metabolic state. Insulin resistance and insulin secretory dysfunction are concurrent pathophysiological factors underlying the development of type 2 diabetes and thus are the targets for primary prevention of the disease. type 2 diabetes is also associated with obesity, and the common link between both is insulin resistance. Approximately 80% of diabetic patients are obese.

The ideal treatment for type 2 diabetes should correct insulin resistance, β-cell dysfunction and normalize hepatic glucose output, as well as prevent, delay, or reverse diabetic complications. To achieve glucose control and prevent diabetic complications, therapeutic agents such as sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones are currently employed. All of these treatments have limited efficacy and are associated with side effects, including weight gain, hypoglycaemia, gastrointestinal disturbances, oedema, etc. Primary prevention of T2DM is emerging as an important strategy. Inhibition of dipeptidyl peptidase-IV (DPP-IV) is one of the promising new targets for the treatment of type 2 diabetes.

Incretins are gut peptides that are released from the gastrointestinal tract in response to nutrient ingestion and promote nutrient assimilation via potentiation of glucose-dependent insulin secretion. Subjects with type 2 diabetes or obesity may exhibit a decrease in the secretion of endogenous incretins, particularly glucagon-like peptide 1 (GLP-1), following food ingestion. Incretin action is rapidly terminated via the action of dipeptidyl peptidase-IV (DPP-IV), which inactivates both glucose-dependent insulinotropic peptide (GIP) and GLP-1 via cleavage at the position 2 alanine.
Inhibition of DPP-IV appears to represent a useful strategy for enhancing the bioactivity of GLP-1 in vivo. Numerous studies have indicated that administration of orally active DPP-IV inhibitors markedly improved metabolism and glucose regulation in animal models of glucose intolerance. In patients with type 2 diabetes, treatment with DPP-IV inhibitors improves insulin secretion and sensitivity, normalizes glucose levels and enhances beta-cell survival.

GRC 8011, a prospective DPP-IV inhibitor, was taken as the test compound to study the in vitro and in vivo efficacy, its pharmacokinetics and toxicity profile. General methodologies followed and research materials and equipment used throughout this thesis work are given in detail in chapter 1. Proof of concept and in vitro profile are established in chapter 2. Enzyme kinetic experiments are done to ascertain the nature of GRC 8011 kinetics and its site of binding on DPP-IV enzyme.

Chapter 3 forms the crux of the entire work wherein the test compound is screened in some of the important animal models to support, validate and substantiate the in vitro observations and the mechanism of action of DPP-IV inhibitors. The experiments included oral glucose tolerance test (OGTT) as an acute primary screening model for antihyperglycaemic activity, followed by pharmacodynamic studies to establish a causal relationship between blood glucose, DPP-IV, GLP-1 and insulin levels and confirm the in vitro findings. Pharmacokinetic profile of GRC 8011 is described in chapter 4. Toxicity (acute and subacute) studies of GRC 8011 conducted in mice are elaborated in chapter 5. GLP-1 agonists slow down gastric emptying, reduce food intake and produce a satiating effect. Effects of GRC 8011 on these parameters are examined in Chapter 6.

Results of all the above studies prove that GRC 8011 is a potential DPP-IV inhibitor that has potential to be a treatment for type 2 diabetes.

Anupindi Raghuram
Biological Research Division, Glenmark Research Centre
Mahape, Navi Mumbai
&
Department of Pharmaceutical Technology
Jadavpur University, Kolkata