3. RATIONALE AND OBJECTIVES

3.1 Drug of choice

Many anti-diabetics and dyslipidemic agents are used in combination for their beneficial synergistic therapeutic action. Drugs were selected in the present study based on suitability, stability and optimum bioavailability.

The following Fixed Dose Combinations (FDC’s) were selected for the study:

1. Glimepiride and atorvastatin calcium\textsuperscript{9,10}.
2. Pioglitazone and simvastatin\textsuperscript{8,11,12}.
3. Glibenclamide and atorvastatin calcium\textsuperscript{13-15}.

3.2 Objective of fixed dose combination

The fundamental need and principles underlying the development and use of fixed dose combination include;

- Improved clinical effectiveness.
- The relative efficiency of reduced dosing regimens (i.e., improved patient compliance).
- Improved patient handling (e.g., nursing or outpatient visits for repeat drug administration) and medical care (e.g., handling of adverse events or side effects).

3.3 Rationale for selection of drugs for fixed dose combination

For the treatment of type 2 diabetes associated with high cholesterol levels, often requires a combination of two or more therapies. Lipid-lowering therapy, especially with statins, has been shown to be beneficial in patients with diabetes. The American diabetes association recommendation and best practice is to use statin therapy, in addition to lifestyle therapy, regardless of baseline lipid levels for patients with diabetes with
apparent cardiovascular disease and patients without cardiovascular disease who are > 40 years of age and have one or more other cardiovascular disease (CVD) risk factors\textsuperscript{16,17}. The FDC’s of - glimepiride with atorvastatin calcium, pioglitazone with simvastatin and glibenclamide with atorvastatin calcium were selected as first-line therapy for improvement of glucose tolerance in type 2 diabetes mellitus associated with dyslipidemia\textsuperscript{17}.

**I. Glimepiride and atorvastatin calcium fixed dose combination**

Patients diagnosed with Type 2 diabetes (T2D) are initially provided with lifestyle advice in order to manage the condition by diet, exercise and weight reduction, followed by treatment with metformin. However, many patients do not gain adequate control of fasting glucose by these methods and other anti-diabetic agents are needed. Furthermore, these patients have an increased cardiovascular risk compared with the general population. Approximately one half of patients with Type 2 diabetes (T2D) die prematurely of a cardiovascular cause and approximately 10\% die of renal failure. Atherogenic dyslipidemia, which is defined as the triad of elevated triglycerides, low High-density lipoprotein cholesterol (HDL-C), and small Low-density lipoprotein cholesterol (LDL-C) particles, is commonly found in individuals with T2D. In diabetic patients, the LDL particles tend to be smaller, denser, and more atherogenic than in the general population. As a result, in patients with diabetes, lowering LDL-C levels may lead to a greater benefit in terms of CVD risk reduction than in patients without diabetes. Multiple clinical trials have demonstrated the significant benefits of lipid-lowering (primarily statin) therapy on CVD outcomes for primary and secondary prevention, irrespective of baseline lipid levels. Hence, clinical treatment guidelines recommend that
patients with T2D should be treated with both an anti-diabetic agent and a statin. Glimepiride is an established once-daily sulphonylurea for use as first-line therapy, and is often used in patients who are metformin intolerant, or in those who are failing to achieve glucose control on metformin monotherapy. Atorvastatin is an established statin that is indicated for reducing the risk of cardiovascular events in diabetic patients, without clinically evident coronary heart disease (CHD), irrespective of whether cholesterol is raised. The risk benefit of both glimepiride and atorvastatin is well established. There is widespread use of both glimepiride and atorvastatin, prescribed separately, in the T2D population. The available literature indicates that there is no drug-drug interaction risk associated with this combination therapy and no clinical Pharmacokinetic (PK) interactions between atorvastatin and glimepiride have been recorded. A once-daily combination product which combines both glimepiride and atorvastatin will fulfill an unmet clinical need in simplifying patient treatment regimens in a patient population who have a significant disease burden$^{9,10}$.

II. Pioglitazone HCl and simvastatin fixed dose combination

The thiazolidinediones (TZDs) are widely used for the treatment of type 2 diabetes. Besides their beneficial effects on insulin resistance and glucose control, TZDs have pleiotropic and anti-inflammatory properties, including modifying the atherogenic LDL profile$^5$. In a recent study (PIOSTAT) with pioglitazone and/or simvastatin therapy in non-diabetic patients with high cardiovascular (CV) risk, showed a significant anti-inflammatory effect of pioglitazone treatment that was comparable to that of simvastatin. The combination of both drugs gave synergistic effects on a broad spectrum of CVD risk factors, particularly high-sensitivity C-reactive protein (hsCRP)$^{11}$. A significant reduction
of LDL-C with simvastatin was observed, but a minor increase of LDL-C with pioglitazone. Simvastatin monotherapy significantly reduced cholesterol and triglyceride concentrations in Intermediate-density lipoprotein (IDL), LDL1 and LDL2. The lipid concentrations and lipid loads in LDL3 remained unchanged. By contrast, treatment with pioglitazone reduced the cholesterol concentration in LDL3 (density 1.040–1.066 kg/l) from 0.38 to 0.31 mmol/l (p = 0.0004) and of the cholesterol load per particle from 1058 to 934 mol/mol (p = 0.0149). Even greater reductions of cholesterol in LDL3 were observed with the combination of pioglitazone and simvastatin: from 0.38 to 0.29 mmol/l (p = 0.0006) and from 1021 to 903 mol/mol (p = 0.0011), respectively. In addition, combination therapy reduced the particle number of LDL3 from 356 to 316 nmol/l (p = 0.0074). Simvastatin preferentially lowered LDL1 and LDL2 subfractions, whereas pioglitazone reduced LDL3 cholesterol and cholesterol load. In addition, the combination reduced the LDL3 particle number. Thus, the data suggest a synergistic action of pioglitazone and simvastatin on atherogenicity of small dense LDL particles.[12]

III. Glibenclamide and atorvastatin calcium fixed dose combination

Atorvastatin co-administration with glibenclamide resulted in enhanced glibenclamide concentration and enhanced glucose reduction. Glibenclamide serum affinity for albumin is 99.8% bound. Metabolic inhibition of glibenclamide by atorvastatin decreases metabolic clearance of glibenclamide and the decreased metabolic clearance may leads to decreased total clearance. Elimination rate of glibenclamide is decreased by its metabolic inhibition with atorvastatin. In diabetic group there is decrease in cyp 3A activity[13,14], diabetes induced decreased cyp 3A activity is further decreased by atorvastatin effect results in significant difference in T_{1/2}. Increase in AUC, C_{max} indicates
the improved bioavailability of glibenclamide in presence of atorvastatin. This may be due to the interaction of atorvastatin with glibenclamide metabolism, i.e., atorvastatin reduces the hepatic metabolism by inhibiting glibenclamide. Thus the action of glibenclamide gets enhanced. The enhanced level of glibenclamide might be responsible for the enhanced secretion of insulin in presence of atorvastatin; additionally it could be combined pharmacodynamics effect since atorvastatin itself improved secretion of insulin\textsuperscript{14,15}. Finally atorvastatin improved the glibenclamide plasma levels which appear to involve in pharmacokinetic as well as pharmacodynamic mechanisms. The blood glucose levels were decreased significantly when glibenclamide is given in combination with atorvastatin\textsuperscript{14}. 
3.4 Objectives of the present investigation

[1] To carry out the pre-formulation studies of the selected drug/s and polymer/s.


[3] To characterize the prepared dosage forms.

