INTRODUCTION
2.0 INTRODUCTION

The use of several drugs is often essential to obtain a desired therapeutic objective or to treat co-existing diseases. Such concomitant use of two or more drugs may result in drug interactions, which may be beneficial, harmful or inconsequential. The knowledge of the pharmacological basis of how one drug may affect the effect of another is useful in deciding those combinations that are beneficial. The administration of one drug can alter the action of another by one of the general mechanisms namely modification of pharmacological action without affecting its concentration in the tissue fluid i.e. pharmacodynamic interaction, or alteration of the concentration that reaches the site of action i.e. pharmacokinetic interaction.

Hypertension is the most common among cardiovascular disorders and not only in the West, but in the Indian subcontinent also, it has been emerging out as the modern age epidemic. It is a common clinical condition that predisposes the affected individual to coronary heart disease, cerebrovascular accidents and heart failure. During the past 2 decades, it has been well documented that hypertension tends to occur in association of other atherogenic risk factors including hyperlipidaemia, diabetes, smoking, obesity, left ventricular hypertrophy, and hyperinsulinaemia. The coexistence of these factors with hypertension increases the risk of coronary heart disease and myocardial infarction.

Leese et al (1996) reported that hypertension and diabetes mellitus co-exist more commonly than would be expected of their individual prevalence. Hypertension is associated with increased mortality due to cardiovascular complications and an increased risk of microvascular complications in patients with diabetes mellitus. They further reported higher incidence of hypertension in diabetic patients, especially non-insulin-dependent diabetes mellitus (NIDDM) ones, when compared with nondiabetic ones. It is also noted that patients with essential
hypertension are prone to develop NIDDM. Further, hypertension and insulin resistance are commonly associated, forming part of the so-called 'Syndrome X' or 'Raeven Syndrome' (Raeven, 1988). Syndrome X is characteristic of many patients with NIDDM, but the underlying mechanisms are not clearly understood (Leese et al., 1996). Once renal disorder due to diabetes develops, hypertension nearly always follows and causes further deterioration in renal function. In recent years, main focus has been on the role of systemic blood pressure in the progression of diabetic renal disease (Rossing et al., 1993). The development of diabetic nephropathy itself is usually associated with hypertension in both insulin-dependent diabetes mellitus (IDDM) and NIDDM patients (Leese et al., 1996).

The last few decades have witnessed many changes in the drug therapy of hypertension. Potentially hazardous drugs with intolerable side-effects have given way to safer and better tolerated drugs. It is now well recognised that heart failure is not merely a disease of the heart, but it is also associated with activation of the adrenergic and renin-angiotensin systems. Because of the pivotal role of the renin-angiotensin system, treatment with angiotensin converting enzyme inhibitors (ACEIs) is now well established as a key component of the optimal pharmacological therapy for patients with hypertension and heart failure. It is also established that ACE inhibition improves symptoms as well as survival in patients with heart failure. Several recent studies have shown that treatment with ACEIs is beneficial in preventing left ventricular remodelling and the onset of heart failure in patients of hypertension and myocardial infarction. Some of these studies have also provided evidence of anti-ischaemic effects of ACE inhibition (Deedwana, 1997) Bakris et al (1996) have suggested that ACEIs have an advantage over other antihypertensive agents in the treatment of patients with hypertension and diabetes mellitus, and especially in those with proteinuria. They further observed that the effects of ACEIs within the kidney are reduction in intraglomerular pressure, improvement in glomerular permeability, prevention of glomerulosclerosis, reduction in mesangial matrix
expansion, increase in natriuresis, reduction in proteinuria etc. The 
ACEIs were shown to improve survival in diabetic nephropathy when 
compared with other antihypertensive agents.

The favourable effects of ACEIs on endothelial function and in 
cardiovascular morbidity are due not only to Angiotensin II (A-II) 
suppression, but also to consequent reduction in bradykinin degradation 
and increased prostaglandin (PG) synthesis (Goldstone et al, 1981; Moore 
The quest for an ideal antihypertensive agent started long back and is 
still on. Among the various classes of antihypertensive agents, ACEIs are 
now a days preferred over others because of their multifaceted beneficial 
effects (Pepine, 1997).

Non-steroidal Anti-inflammatory Drugs (NSAIDs) have analgesic, 
antipyretic and anti-inflammatory effects. They exert these effects by 
inhibiting the enzyme cyclooxygenase, which takes part in the formation 
of PGs. NSAIDs like aspirin, diclofenac sodium, mefenamic acid, 
piroxicam etc. have been used for severe painful inflammatory conditions 
like rheumatoid arthritis, osteoarthritis, ankylosing spondylosis as well 
as injury-generated pain and inflammation with or without pyrexia (Insel, 
1996). Apart from these, role of aspirin as antiplatelet agent is now well 
established. It helps in preventing cardiovascular complications (ISIS-2, 
1988), but whether or not this effect is shared by other NSAIDs, is yet to 
be determined through clinical studies.

The enzyme cyclooxygenase (COX) has two subtypes—COX-1 and COX-2 
and the conventional NSAIDs block both of them (Jouzeau et al, 1997). 
Despite specific COX-2 inhibitors like nimesulide, celecoxib, rofecoxib 
e etc. being available in Indian market, diclofenac sodium is being used to 
a great extent in the patients of arthritis with or without hypertension 
and/or diabetes mellitus.

Now a days, the therapy which is generally resorted to in the treatment of 
hypertension or cardiac failure is the multiple drug therapy by most of
the clinicians, rightly for greater efficacy. Co-administration of low-dose aspirin with antihypertensive drugs has become a common feature in clinical practice for the prophylaxis of cardiovascular complications viz. coronary heart disease or stroke. But, if the patient has been suffering simultaneously from hypertension (with or without diabetes mellitus) and joint disorders like osteoarthritis or rheumatoid arthritis, then along with an ACEI, NSAID like diclofenac sodium is co-prescribed. Both the medications have to be consumed for a long time. Reports are not scarce about the attenuation of antihypertensive effect of ACEIs by concomitant treatment with NSAIDs. Aspirin has been reported to attenuate the antihypertensive effect of captopril (Moore et al, 1981). Similar interactions have been reported in case of captopril-indomethacin (Ogihara et al, 1981; Silberbauer et al, 1982; Swartz & Williams, 1982; Witzgall et al, 1982; Dzau et al, 1984), captopril-ibuprofen (Goldstone et al, 1981), captopril-sulindac (Salvetti et al, 1982), enalapril-indomethacin (Oparil et al, 1983), lisinopril-sulindac (Salvetti et al, 1987) and, enalapril-aspirin (Guazzi et al, 1998) combinations. However, the effects of co-administration of diclofenac sodium and ACEIs in hypertensive patients (with or without diabetes mellitus) on blood pressure control and on biochemical parameters are not well studied. Therefore, in the present study, an attempt has been made to study the effects of combining diclofenac sodium with enalapril or lisinopril on blood pressure, insulin sensitivity, platelet aggregation, renal function, hepatic function and lipid profile in hypertensive arthritic patients (with or without diabetes mellitus).