While performing the vital function of gas exchange, airborne pathogens and environmental pollutants also make their entry into the lungs. The first cells to encounter the inhaled foreign material, reaching the lower respiratory tract, are the resident macrophages called as 'alveolar macrophages'. Alveolar macrophages (AMs) maintain the sterility of the lower respiratory tract and prevent the injury to the lung tissue. When activated, these AMs release a variety of biologically active compounds such as cytokines, free radicals, proteases and other lysosomal enzymes. These chemical mediators participate in the generation of immune response and killing of invading pathogens. With the continuous exposure to environmental insults, the AMs remain in an activated state and thus may contribute to lung injury. Among the various chemical mediators, reactive oxygen species (ROS) e.g. superoxide anion (O$_2^-$), H$_2$O$_2$ and reactive nitrogen intermediates (RNI) like nitric oxide, peroxynitrite are potent damaging moieties and play a role in pathophysiology of inflammation-induced tissue injury. ROS are generally unstable, very reactive and act as chain carriers in chemical reactions. Superoxide is the first toxic oxygen derivative produced during respiratory burst. It is however, soon converted into H$_2$O$_2$, enzymatically or non-enzymatically. In the presence of catalytic quantities of transition metals, O$_2^-$ and H$_2$O$_2$ may react to form the highly reactive hydroxyl radicals (OH). ROS are capable of inflicting reversible or irreversible damage to the compounds of all biological classes including nucleic acids, proteins, lipids, lipoproteins and connective tissue molecules. ROS are also involved in the modulation of intracellular signals, such as calcium pathway, nuclear factor kappa B (NF-κB) pathway and in the regulation of certain oncoproteins (Abate et al., 1990; Cerutti & Trump, 1991; Schreck & Baeurele, 1994). Nitric oxide can react with amines to produce carcinogenic N-nitroso-compounds. These N-nitroso compounds possess the tumor initiating and tumor promoting potentials In view of all these facts, it is not surprising to note that ROS and RNI have been found to be involved in a wide variety of lung diseases...
viz. adult respiratory distress syndrome (ARDS), asthma, fibrotic lung disorders, ischemia-reperfusion lung injury, hyperoxia and lung cancer.

All tissues are vulnerable to oxidant damage. The oxidant burden occurs as a by-product of cellular oxidative metabolism, which in the lung is further increased by inhaled toxic particles, gases and cigarette smoke (Cross & Halliwell, 1991). In addition to inhaled oxidants, the epithelial surface is at risk of oxidant mediated attack by activated phagocytes. Thus, the discovery that inflammatory phagocytes produce large quantities of ROS provides the basis for the hypothesis by which inflammation and carcinogenesis might be related, that is, ROS generated by inflammatory phagocytes can cause injury to target cells which may contribute to cancer development.

Macrophages release enhanced levels of ROS, NO⁻ and n-nitroso-compounds TNF-α, IL-1 in response to endotoxin challenge. Bacterial LPS is one of the most commonly encountered agents known to activate the macrophages. It is widely recognised that LPS exposure occurs via respiratory and systemic G-ve bacterial infections (Brun Buisson et al., 1995; Wenzel et al., 1996). Humans are frequently exposed to indigenous G-ve gut flora through gastrointestinal (GI) tract translocation i.e. passage of LPS from GI lumen into blood (Jacob et al., 1970). Elevated respiratory exposure to LPS occurs in a variety of occupational environments. These include grain processing (Dosman et al., 1981), waste treatment plants (Mattsby et al., 1989), poultry and swine industries (Donham et al., 1989), office and household air (Jussila et al., 2001).

Moreover, macrophages express receptors for the primary proinflammatory cytokines like TNF-α, IL-1, which subsequently activate macrophages in an autocrine way. Although AMs try to minimise the inflammatory response in the lung, yet with the continuous environmental or pathogenic insult, the activated AMs may fail to prevent the generation of inflammatory response and inflammation associated damage. Rather, AMs may further aggravate the damage by producing ROS, NO⁻, chemotactic factors for neutrophils, profibrotic mediators and mediators, which are capable of injuring the lung parenchyma. Thus, AMs can amplify and perpetuate the inflammation. The inappropriate release of ROS and NO⁻ into the alveolar environment may
cause injury to the delicate alveolar tissue. Thus, the ability of a drug to regulate the production and/or release of these species by AMs would be highly advantageous to the host. Moreover, as these cells produce increased amounts of free radicals during activation, it seems possible that in the process they might damage themselves also, as has been reported in isolated human peripheral polymorphonuclear leukocytes (McCord & Salin, 1977). The self-inflicted damage to leukocytes was manifested by cell death. Taking into consideration the role of activated AMs in prolonging inflammation and its related damages through the production of ROS and RNI, it is understandable that their physiology could be modified to regulate the release of these species.

To protect themselves against the oxidative damage caused by the reactive oxygen species (ROS), cells have evolved a network of protective enzymes and antioxidants, which prevent or intervene in the injurious oxidative reactions initiated by these species. Antioxidant enzymes include superoxide dismutase (SOD), catalase, glutathione reductase (GR) and glutathione peroxidase (GpX). All the more important is low molecular weight non-enzymatic antioxidant reduced glutathione (GSH), which is an important intra as well as an extracellular endogenous antioxidant. These antioxidants prevent the formation of free radicals, convert oxidants to less toxic species, compartmentalise ROS away from vital cellular structures, repair molecular injury induced by free radicals or modify the enzyme molecules. For a cell like an alveolar macrophage, which resides in aerobic environment, the importance of antioxidant defense system becomes all the more important.

Our immune system tends to overact to any minute challenge. The phagocytes are programmed for overkill, not for caution, but because so much is at risk, if they fail to carry out their mission. Our ingenuity enables us to treat ourselves with more targeted synthetic drugs to attenuate selectively the inflammatory response to spare body from the damage associated with it. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed and consumed drugs for the purpose. Their major mechanisms of action are inhibition of cyclooxygenase (COX) enzymes responsible for arachidonic acid metabolism and generation of lipid mediators of inflammation like prostaglandins,
leukotriens etc. Recent studies have shown that NSAIDs may act by mechanisms other than COX inhibition, i.e. inhibiting expression of cell adhesion molecules, inhibiting the release of cytokines and ROS by neutrophils. Nimesulide is one of the selective COX-2 inhibitor and is most commonly used in India. It has been shown to be the inhibitor of cytokine release, cytokines or phorbol myristate acetate (PMA) induced release of prostaglandins etc., but the studies regarding the effects of nimesulide consumption on ROS and RNI release by alveolar macrophages under lung inflammatory conditions are totally lacking. The drug has also shown anticarcinogenic potential in some experimental models. The present work was therefore designed to explore the effects of nimesulide on the functions of AMs and also to study the antioxidant effects of the drug on AMs and major tissues like liver, lungs and kidneys, with the following aims and objectives.

**Aim**: To investigate the *in vitro* and *in vivo* effects of nimesulide on oxidant/antioxidant functions of alveolar macrophages and the major tissues in rats under lung inflammatory conditions.

**Objectives**

1. To study the antiradical and antioxidant activities of nimesulide.
2. To investigate the effects of nimesulide on ROS release and oxidative stress in elicited rat alveolar macrophages.
3. To evaluate the impact of nimesulide administration on the functions of AMs of rats intratracheally instilled with LPS.
4. To study the effect of nimesulide on the antioxidant defense system and oxidative stress in AMs of rats challenged with LPS.
5. To study the impact of nimesulide and LPS on antioxidant defense system and oxidative stress in lungs, liver and kidneys.
6. To evaluate the impact of nimesulide on hepatic drug metabolising system of rat.