Preface

The current processes of developing new drugs or medicinal products are insufficiently efficient. Circa, from our literature review based understanding, for every 5,000 to 10,000 molecules that enter the research and development pipeline, approximately 250 molecules enter the preclinical program, five are tested in clinical trials, and only one receives approval for market introduction. Considering the fact that oral ingestion is the most convenient and commonly employed route of drug delivery, the two most important failure causing problems are drug solubility and permeability, as they determine to a large extent the oral bioavailability of a drug substance. According to the literature, between 60 and 70% of the APIs in the pipeline show sufficient membrane permeability but a low water solubility. Poor solubility leads to the failure of many drug candidates because poor bioavailability, limited by the solubility of the final drug is a common problem that occurs during drug development. Substantial amount of time and effort is spent on improving the solubility of drugs without tampering with their molecular structure or altering the biological activity. A smart formulation can rescue the drug development projects.

Ezetimibe (Eze) is a model low soluble and highly permeable drug. Pharmacologically, Eze is a hypocholesterolemic agent. The oral absorption of Eze shows inter-subject variability and its bioavailability could be as low as 35% due to its poor solubility and P-gp efflux. So far, Eze has been formulated as cyclodextrin (CD) complexes, cocrystal (CoC) formulations and colloidal drug delivery systems (CDDS). While the studies on CD complexes and CoC formulations were limited only to *in-vitro* characterization, the CDDS formulations were studied extensively at *in-vivo* level too. So, the *in-vivo* behavior of Eze CD complexes and CoC systems lacked an in-depth study report. The CDDS formulations reported improvement in *in-vitro* dissolution as well as *in-vivo* bioavailability of Eze which signified the effect of nanosize on the improved performance of Eze. But, the CDDS formulations reported so far contained several components and involved laborious and time taking preparation methods. So, though nanosize proved advantageous in improving the performance of Eze, there is still a need to develop a simpler, less toxic, less laborious and economic nanoformulation.

Therefore, to fill the left out gaps and to meet the unmet needs, there is a necessity to develop more potent formulations to deliver Eze with acceptable bioavailability. The idea of the work done in the present thesis was conceived based on the above discussed topics and problems. The study was designed with an objective to develop new and simple formulations capable of addressing the possible unmet needs of the previous research works. The basic requirement in designing a suitable formulation for a particular drug involves use of minimum number of excipients with the easiest possible technology in order to keep the cost of the formulation development as low as possible. In this context, a thorough literature survey was conducted with special emphasis on different formulation technologies currently employed in the development and production of pharmaceutical oral dosage forms.

The entire research work was carried out systematically in four sequential steps. First, an elaborate attempt was made to explore the cocrystallization formulation approach. Second, an involved effort was made to study the ternary CD complexation formulation approach. Third, a detailed endeavor was made to study the drug nanocrystallization formulation approach. The formulations developed were subjected to detailed physiochemical characterization, pharmacokinetic and pharmacodynamic evaluation in rats and the results were discussed in-depth. Further, as the fourth step, one optimized formulation from each of the above steps was chosen for comparison with a marketed tablet product. Also, the optimized formulations were compared with each other to arrive at the formulation approach that improved the bioavailability and therapeutic efficacy of Eze to the most.

The purpose of this study was to introduce to the pharmaceutical researchers and industry, a new avenue for the development of alternative and advantageous formulations to improve the aqueous solubility, achieve desired drug release and pharmacokinetic profile and thus impart enhanced therapeutic value to the drug chosen for this study, Eze.