CHAPTER – 9

Conclusions

The oral route of administration is the most commonly preferred route for the delivery of a large number of important drugs in various therapeutic areas, and many patients prefer standard oral dosage forms as well as advanced oral drug delivery systems over other dosage forms. This preference is because of various factors such as the non-invasiveness, ease-of-use, and reliability of oral dosage forms. The major problem faced in designing oral dosage forms is low bioavailability and unfortunately, the number of poorly soluble BCS class II drugs that exhibit a poor oral bioavailability is steadily increasing. The introduction of large numbers of poorly bioavailable drugs creates the demand for updated pharmaceutical formulation technologies to meet the associated challenges. The market for formulation technologies is likely to increase because improvements in the technologies have provided new directions for product development. Accordingly, scientists have been pushing the boundaries of oral drug delivery for many decades. However, there is no universal technology that may be appropriate for all poorly soluble drugs.

In the present research work, an attempt was made to improve the oral bioavailability of a BCS class II antihypercholesterolemic agent, Eze, by formulating CoCs, CD ternary complexes and NCs. Since Eze is a hypocholesterolemic agent, development of suitable formulations to improve the oral bioavailability of Eze may find scope in treating the hypercholesterolemic conditions and the associated coronary heart diseases (CHDs) like atherosclerosis. Modification of risk factors such as hyperlipidemia may be beneficial in

slowing the atherosclerotic process and preventing cardiovascular mortality. Cholesterol is an essential part of every cell in the body. The unwanted high cholesterol levels in plasma may be due to increased uptake of exogenous cholesterol and subsequent deposition and decreased cholesterol catabolism as evidenced by a reduction in bile acid production and turnover of bile acids. Therapeutic lifestyle changes include dietary changes, weight reduction, and increased physical activity. For those patients who are at higher risk of CHD, LDL lowering drug therapy may be essential.

Eze is the first of a new class of lipid-lowering drugs known as cholesterol absorption inhibitors. Eze localizes at the brush border of the small intestine and selectively inhibits the absorption of cholesterol from the intestinal lumen into enterocytes. Eze does not affect absorption of fatty acids, bile acids, or fat-soluble vitamins, including vitamins A, D, E, and K and α and β carotenes.

After oral administration, Eze is rapidly glucuronidated in the intestine, and once glucuronidated, it undergoes enterohepatic recirculation which repeatedly delivers the drug to its site of action. Notably, the glucuronide of Eze is even more potent as a cholesterol absorption inhibitor than the parent compound, possibly because of its localization in the intestine. The enterohepatic recirculation ensures long duration of action of the drug. Eze is commercially available as a once a daily immediate release tablet product. The timing of dosing does not affect its activity, and food does not affect its bioavailability. In animal models, Eze decreased delivery of cholesterol from the intestine to the liver, reduced hepatic cholesterol stores, up-regulated LDL cholesterol receptors on liver cell membranes, and increased clearance of cholesterol from blood. However, the oral bioavailability of this beneficial drug, Eze, is lowered to as low as 35% predominantly due to its low aqueous solubility and P-gp efflux.

A thorough literature survey was conducted before beginning this research work by placing a special emphasis on different formulation technologies currently employed in the development and production of pharmaceutical oral dosage forms. As far as the drug chosen for the present study, Eze was concerned, the drug was until now formulated as cocrystal (CoC) formulations [Snehal et al., 2012], cyclodextrin (CD) complexes [Patel et al., 2008], and colloidal drug delivery systems (CDDS) [Bandyopadhyay et al., 2012; Dixit and Nagarsenker, 2008; Bali et al., 2010 and 2011]. The left out gaps and the unmet needs of the previous research works were already pointed in the previous chapters of this thesis. The present study was designed with an objective to develop new and simple formulations capable of filling the left out gaps and addressing the possible unmet needs of the previous research works.

The present investigation aimed to improve the oral bioavailability and therapeutic efficacy of Eze by employing three formulation approaches namely, cocrystallization, CD ternary complexation and nanonization. Accordingly, Eze CoCs were prepared using NA and ND as coformers for the first time (chapter 5); CD ternary complexes of Eze were prepared with HPBCD using TPGS/AA2G as ternary substance for the first time (chapter 6); and Eze NCs were prepared using TPGS and AA2G as stabilizers for the first time (chapter 7). The detailed and systematic procedures followed to optimize the formulations under each of the formulation approach and the observed results from the characterization studies have already been elaborately summarized at the end of each of the formulation specific chapter (chapter 5, 6 and 7).

Eze is a hypocholesterolemic drug and the problems that affect its bioavailability are its low water solubility and P-gp substrate nature. The excipients employed in this study to formulate Eze were hydrophilic with or without additional potentials like P-gp

inhibitory action or hypocholesterolemic action. Thus, the current research work aimed to improve the low oral bioavailability of Eze by formulating CoCs, CD ternary complexes and NCs, employing suitable - likely problem solving excipients. It has been hypothesized that the selected formulations may serve to not only improve the solubility and dissolution properties of Eze *in-vitro* but also to enhance the *in-vivo* performance of Eze by either offering a synergistic hypocholesterolemic effect or improving its *in-vivo* absorption at the small intestinal brush border.

Briefly, it may be concluded that the present study successfully developed three different and facile formulation approaches to improve the *in-vitro* and *in-vivo* performance of Eze. The following were the significant findings of this research work:

- NA and ND are novel coformers to generate Eze CoCs;
- AA2G and TPGS are beneficial ternary components to Eze-CD systems [Srivalli and Mishra, 2016]; and
- AA2G and TPGS are suitable NC stabilizers for Eze [Srivalli and Mishra, 2015b].

As hypothesized, all the prepared formulations successfully served not only in improving the *in-vitro* properties of Eze but also in enhancing its *in-vivo* performance. All the formulations were characterized at *in-vitro* and *in-vivo* levels and one optimized formulation was filtered for each of the applied formulation approach. A pharmaceutical CoC, Eze-ND, a ternary CD complex, E-CD-TPGS and a drug NC formulation, ESTNC F8, were identified as quite potential oral formulations in effectively improving the *in-vitro* and *in-vivo* performance of Eze. All these optimized formulations were further compared at *in-vitro* and *in-vivo* levels with each other as well as with a marketed tablet, Ezentia, to propose the most suitable formulation approach to deliver Eze with highest

bioavailability. Additionally, the dose reduction efficiencies offered by each of the above mentioned three optimized formulations were studied and reported (chapter 8) in terms of the ability of each of the optimized formulation to manage the plasma lipids and atherogenic indices. The solubility and dissolution properties of all the three optimized formulations were superior to pure drug. The bioavailability of Eze-ND or E-CD-TPGS or ESTNC F8, was superior to the pure drug and the marketed tablet product. The therapeutic efficacies of Eze-ND and E-CD-TPGS were higher than pure drug or marketed tablet product even after half dose reduction while the therapeutic efficacy of ESTNC F8 was higher even after five times dose reduction.

The primary objective of a formulation research work is and remains to design a most suitable formulation for a particular drug which involves use of minimum number of excipients and easiest possible technology so as to keep the cost of development as low as possible. In the present research work, NCs was identified as the most suitable formulation approach and TPGS based NCs was identified as rational, simple, economic, and promising oral formulation for improving the *in-vitro* and *in-vivo* performance of Eze. ESTNCs, the electrostatically stabilized TPGS NCs were identified as the most suitable formulation as they produced maximum enhancement in aqueous solubility, dissolution, bioavailability and therapeutic efficacy of Eze.