The salient outcomes of the present research work carried out under the project, “Design, Development and Systematic Optimization of Novel Oral Drug Delivery Systems of Ezetimibe and Valsartan with Enhanced Bioavailability Potential” are enumerated as under:

**Liquid and supersaturable self-emulsifying drug delivery systems of ezetimibe**

- Based on preliminary solubility studies and ternary phase diagrams, Capryol 90 and Tween 80 for MCT-SEDDS and Maisine 35-1 and Labrasol for LCT-SEDDS were selected for further studies. Equilibrium phase behavior and emulsifying ability of emulgents viz. Cremophor EL, Labrasol and Tween 80, Tween® 40 were evaluated and discerned by plotting ternary phase diagrams, the most promising results were obtained with Labrasol for LCT-SEDDS and Tween 80 for MCT-SEDDS.

- As a prelude to systematic formulation development and optimization, screening studies were conducted to embark upon selection of judicious influential factor variables employing Taguchi design. The studies indicated lipids (i.e., Maisine 35-1 and Capryol 90) and emulgents (i.e., Labrasol and Tween 80) to be the most influential factors in formulation of liquid SEDDS. Studies employing FTIR ruled out any plausibility of physicochemical incompatibility between the drug and the investigated excipients. Hence, FbD optimization employing these two factors was considered imperative for attaining the optimized MCT-SEDDS and LCT-SEDDS formulations.

- The chosen experimental design for Formulation by Design (FbD), i.e., central composite design (CCD), mathematical model for generation of polynomials, i.e., multiple linear regression analysis (MLRA), and the methods for location of optima i.e., brute-force, overlay plots and desirability function, all successfully vouched the appropriate selection of the optimized formulations, i.e. OPT-LCT SNEDDS containing 286 mg of Maisine 35-1 and 500 mg of Labrasol and OPT-MCT SNEDDS containing 420 mg of Capryol 90 and 500 mg of Tween 80, to be the most influential factors in formulation The said formulations fulfilled all the desired criteria of high
5. CONCLUSIONS

Qi5min, reduced Dnm, high Perm5min, minimum T_evol, adequate %DE30min, and MDT. Validation of FbD studies distinctly demonstrated the accuracy, validity and finally high prognostic ability of the proposed model in the prediction of studied response variables.

- Accelerated stability analysis of the optimized SNEDDS formulations indicated minimal degradation from the formulation stored at 40°C ± 2°C/75% RH ± 5% RH.

- Long term stability studies indicated drug precipitation from OPT-LCT SNEDDS around 9 months of study and thus a special type of SEDDS, i.e., supersaturable systems was endeavored in order to control the drug precipitation.

- Globule size of the optimized formulations, i.e., OPT-LCT and OPT-MCT 54.07 nm and 65.88 nm, respectively indicating the preparation of SNEDDS. The zeta potential of the optimized formulations, i.e., OPT-LCT and OPT-MCT were observed to be −38.76 mV and −34.98 mV, respectively indicates enhanced stability of the formulations.

- Various PPI's viz. HPMC E4M, E5LV, E15LV, E50LV, and PVP K25 and K17PF were explored in order to observe their ability to attain the state of supersaturation. Afterwards, equilibrium solubility, degree of supersaturation and supersaturation index were calculated and the excipients followed the order:

  HPMC E5LV > HPMC E4M ~ HPMC E15LV > HPMC E50LV > PVP 17PF > PVP K25

  For the formulation of S-SNEDDS, HPMC E50 LV at 5%w/w exhibited excellent results by maintaining a high concentration of ezetimibe in solution for 90 min.

- The rheograms obtained for LCT-SNEDDS, MCT-SNEDDS and S-SNEDDS indicated that increasing the shear rate and shear stress, the absolute viscosity of the optimized formulations remains around 0.10 to 0.12 Pas indicating Newtonian type of flow.
5. CONCLUSIONS

- Comparison of optimized MCT-SNEDDS and LCT-SNEDDS formulations with that of the marketed brand (Ezedoc) and pure drug, indicated the marked supremacy of SEDDS, with several-fold improvement in dissolution parameters. Drug release results obtained followed the order: S-SNEDDS > MCT-SEDDS ~ LCT-SEDDS > HP-β-CD > Ezedoc > pure drug.

- *In vivo* pharmacodynamic studies for estimating hypolipidemic effect of various formulations were conducted using plasma samples obtained from SD rats. Various types of lipid levels were estimated which indicated significant modification in TG, TC, HDL, LDL and VLDL vis-à-vis the conventional marketed formulation (Ezedoc).

- *In situ* single pass intestinal perfusion (SPIP) technique in Wistar rats were carried out to determine the augmentation of the permeability and absorption potential of the drug. Highly significant increase in permeability and absorption parameters infer the sagacious use of such SNEDDS formulations for dissolution as well as permeation improvement of drugs.

Liquid and cationic self-emulsifying drug delivery systems of valsartan

- A new method of reversed phase HPLC using PDA detector was developed and validated for quantitative estimation of valsartan in mobile phase as well rat plasma samples. The results exhibited excellent linearity, accuracy, precision and robustness with low values of LOD and LOQ.

- Initial equilibrium solubility studies and ternary phase plots revealed Capmul MCM L8 and Tween 80 as constituents for MCT-SEDDS while Lauroglycol FCC and Tween 40 as excipients for LCT-SEDDS. Both of these formulations were investigated for further studies.

- Influential formulation and process parameters were chosen analyzing several possible variables employing two different types of screening designs, i.e., fractional factorial design (FFD) for LCT-SEDDS and Plackett-Burman design (PBD) for MCT-SEDDS. Results obtained from FFD screening design indicated the importance of Lauroglycol FCC and Tween 40 for formulation of LCT-SEDDS. In case of MCT-SEDDS, Capmul MCM L8 and

459
5. CONCLUSIONS

Tween 80 were found to significantly influence the parameters while screening them using PBD design.

- The formulation containing 225 mg of Lauroglycol FCC and 560 mg of Tween 40 was selected as the optimal LCT-SEDDS formulation. Likewise, for the formulation of optimized MCT-SEDDS, 340 mg of Capmul MCM L8 and 850 mg of Tween 80 was selected. Both type of SEDDS formulation fulfilled all the desired criteria of increased Q_{15\text{min}} increased, reduced D_{\text{nm}}, enhanced Perm_{45\text{min}}, lower T_{\text{emul}}, adequate %DE_{30\text{min}} and MDT. Drug release of optimized formulations was found to be far more regulated than that of the conventional marketed formulation. Validation of FbD studies demonstrated high prognostic ability of the proposed experimental design.

- Accelerated stability analysis of the optimized SNEDDS formulations indicated minimal degradation from the formulation stored at 40°C ± 2°C/75% RH ± 5% RH.

- Long term stability studies of the optimized SNEDDS formulations at the standard temperature and humidity conditions are under observations.

- Globule size of the optimized SEDDS formulations, i.e., OPT-LCT and OPT-MCT were found to be 12.11 nm and 63.20 nm, respectively construing the formation of SNEDDS. High values of zeta potential, i.e., -40.82 mV and -27.06 mV, respectively for OPT-LCT and OPT-MCT indicated high stability of the optimized formulations.

- During the optimization studies employing FbD, one of the variables, i.e., %Perm_{45\text{min}} was observed to be sufficiently low. Hence, in order to enhance the permeation of MCT-SNEDDS, different cationic charge inducers, i.e., stearylamine, chitosan and oleylamine were explored.

- For the formulation of C-MCT SNEDDS, oleylamine in the concentration of 5%w/v exhibited excellent permeation results.

- Upon varying the shear rate and shear stress, the absolute viscosity of the optimized formulations were observed to be in the range of 0.25 to 0.38 Pas indicating Newtonian type of flow.
5. CONCLUSIONS

- In vitro drug release studies indicated superiority of optimized MCT-SEDDS and LCT-SEDDS formulations over the marketed brand (Valzaar) and pure drug. The results showed several-fold improvement in dissolution parameters. Drug release results obtained followed the order:

  LCT-SEDDS ~ C-LCT SNEDDS > MCT-SEDDS > C-MCT SNEDDS > Valzaar > pure drug

- The results obtained from SPIP studies in Wistar rats revealed distinct augmentation in permeability and absorption potential of the optimized formulations, especially, the cationic form of MCT-SNEDDS.

- *In vivo* pharmacokinetic studies carried out in rats indicated that the plasma drug profile of animals administered with the optimized SNEDDS formulations were able to significantly augment of the oral bioavailability of valsartan in comparison to marketed immediate release formulation.

- Various levels of IVIVC (i.e., level A, level B, level C and level D) were established with varying statistical significant corroborating the rational selection of *in vitro* dissolution conditions (i.e., medium, apparatus, etc) to simulate the *in vivo* pharmacokinetic parameters.

In a nutshell, the present work reports the formulation development of various kinds of systematically FbD-optimized SNEDDS formulations of ezetimibe and valsartan successfully and demonstrates the bioavailability enhancement potential in animals using principles of pharmacokinetic and pharmacodynamic studies. The techniques employed during the current work can be extrapolated to other BCS class II drugs with analogous configurations and related biological issues.