CHAPTER 5
Summary and Conclusion

5.1 Summary of the Work

Hypertension is a major contributor to the global disease burden, occurring as an insidious accompaniment to aging populations [1, 2]. Hypertension management aims to reduce the long-term risk of cardiovascular complications and involves lifestyle modifications and antihypertensive drug therapy. In recent years, increasing attention has been focused on SNEDDS to facilitate oral administration. The absolute bioavailability of Lercanidipine is about 10%, because of the high first-pass metabolism in the fed condition of the patient [3].

According to the 2004 US Renal Data Report, more than 300,000 patients with end-stage renal disease (ESRD) require dialysis. In spite of sensational advances in drug, the death rate for patients with ESRD remains more than 20% every year [4]. Optional hyperparathyroidism is a genuine entanglement of dialysis and can prompt renal osteodystrophy and other organ dysfunctions [5, 6]. Cinacalcet is demonstrated for the treatment of hypercalcemia in patients with parathyroid carcinoma or for auxiliary hyperparathyroidism in patients with ceaseless kidney sickness who require dialysis [7]. In some embodiments; it was found that the nanoparticulate Cinacalcet compositions exhibit improved bioavailability as compared to known non-nanoparticulate Cinacalcet compositions [8].

In the present study, an attempt was made to enhance the solubility, stability and \textit{in vitro} drug diffusion of two BCS class II drugs namely Lercanidipine HCL and Cinacalcet HCL.
by formulating them as SNEDDS. The developed formulations were characterized by various parameters for its ability to form nanoemulsion. Lercanidipine HCL and Cinacalcet HCL have log P of 6.4 [9] and 6.5[10], respectively making both the drugs suitable candidates for the development of SNEDDS.

Analytical methods were developed for chosen drugs for the estimation of the drug in formulations. Samples of received drugs and excipients were subjected to identification and compatibility study by FTIR. Based on drug solubility in various solvents and their blends, SNEDDS were prepared. The present research was aimed to explore SNEDDS formulation development of Lercanidipine HCL and Cinacalcet HCL using $3^2$ factorial design for improvement in drug diffusion compared to marketed formulation of Lercanidipine HCL and Cinacalcet HCL respectively. The present research also described detailing advancement of stable SNEDDS of Lercanidipine and Cinacalcet HCL using oil and surfactant/co surfactant on the basis of preliminary trials.

The $3^2$ factorial design was utilized with various concentration of oil and surfactant and co surfactant as independent factors. The dispersion time, globule size and medication discharge for Lercanidipine HCL and Cinacalcet HCL were chosen as dependent factors. The optimized batch was selected on the basis of arbitrary criteria using Design Expert software. The data obtained were statistically analysed by ANOVA and model equations were generated and contour plots as well as 3D surface plots were constructed for each response. Optimized formulation assessed by different parameters like particle size, polydispersity index, zeta potential, solubility and in vitro diffusion study. The composition of optimized formulation containing Lercanidipine HCL and Cinacalcet HCL showed that drug diffusion was significantly dependent on selected independent factors. Optimized formulations were subjected to short term accelerated stability study according to ICH guidelines. The developed formulations were found stable under tested stability conditions.

### 5.2 Achievements with Respect to Objectives

- The solubility of both BCS class II drugs were enhanced.
- FTIR study revealed that all the excipients used were compatible with drugs.
➢ The globule size (less than 100 nm), zeta potential (toward the highest negative side) and PDI (less than 0.3) of optimal formulations fitted in criteria of ideal SNEDDS.

➢ The data analysis of $3^2$ full factorial design used for an optimization of SNEDDS formulations revealed that the values of selected responses were strongly dependent on the selected independent variables.

➢ The in vitro study revealed that diffusion of drugs were greatly enhanced by SNEDDS formulation.

➢ The optimal formulations had the maximum diffusion rate as compared to the marketed drugs and pure drugs.

➢ Stability studies revealed that the formulations were found stable under tested stability conditions.

### 5.3 Major Contribution and Practical Implications of the Work to Society

Hypertension is a worldwide burden. Hypertension is one of the main sources for mortality, as it might be asymptomatic however a considerable measure of confusions will grow quickly and prompting demise. Anticipation and control of hypertension diminishes mortality, and heart failure.

Secondary hyperparathyroidism is a serious complication of end-stage renal disease and can lead to renal osteodystrophy and other organ failure. Management of deadly parathyroid carcinoma presents a challenge because effective medical therapy was not available. Cinacalcet is a drug of choice for the treatment of hypercalcemia in patients with parathyroid carcinoma or for auxiliary hyperparathyroidism in patients with ceaseless kidney sickness who require dialysis.

Based on the results obtained for conducted research, it was concluded that the proposed objective of the research work of enhancing bioavailability of Lercanidipine HCL and Cinacalcet HCL was achieved and it can be applied for other drugs of the BCS class II.
Present investigation on SNEDDS of antihypertensive and calcimimetic drugs explored the possibility of efficacious treatments with dose reduction and dosing frequency for their administration by oral route. Subsequently, further examinations with improvement and assessment of nanoformulations of different medications ought to be directed. The nanoformulation approach opens new therapeutic strategies for other diseases for enhancing treatment success rates.

### 5.4 Recommendations for Future Research

The present investigation was aimed for SNEDDS delivery system intended to be administered through oral route. Reasonable model for other pharmaceutical medications ought to be created to evaluate the scope of medication by oral route and their adequacy. The formulation technique utilized has feasibility for scale-up on industrial scale. Hence, after clinical trials and fulfilment of other regulatory requirements, the created formulation has great degree for commercialization and may turn out to be a help to the general public.

### 5.5 Conclusion

Pharmaceutical drugs which belong to BCS class II have poor oral bioavailability due to their limited aqueous solubilities. With the present investigations, it may be concluded that SNEDDS of a poorly soluble drug Lercanidipine HCL and Cinacalcet HCL were successfully developed and optimized using the systematic approach of design of experiments (DoE).

Various preliminary experiments were performed for selection of suitable excipients and formulation technique. Various oils and surfactants and co surfactant were screened primarily on the basis of solubility of the drug and dispersion time with different surfactants in trial batches. The compatibility of the excipients with the drug was assured with FTIR spectroscopy. SNEDDS were prepared using a systematic approach of design of experiments. After the preliminary experiments, a $3^2$ factorial design used with dispersion time, particle size and drug diffusion as response variables using Design Expert 11 software (Stat-Ease, Inc., USA). The data were statistically analysed by ANOVA and model equations were generated and contour plots as well as 3D surface plots were constructed.
for each response. Optimized SNEDDS was evaluated for particle size, polydispersity index and zeta potential. In this research, an endeavour was made to create stable SNEDDS to upgrade oral bioavailability of chosen drugs. Thus, the fundamental was to plan and create nanoemulsion of selected drugs with the goal to increase the bioavailability. Suitable analytical methods were selected for determining in vitro diffusion study. Optimized formulations were subjected to accelerated stability study according to ICH guidelines and the formulations were found stable under tested stability conditions.

Lercanidipine HCL is an orally administered ACE inhibitor and Cinacalcet HCL is a calcimimetic drug with poor solubility, stability and oral bioavailability. The objective of our investigation was to formulate self nanoemulsifying drug delivery system (SNEDDS) of Lercanidipine HCL and Cinacalcet HCL using oil, surfactant and co surfactant that could improve its solubility, stability and oral bioavailability. The composition of optimized formulation consists of Capmul MCM as oil, Polysorbate 20 as surfactant and Transcutol P as co surfactant, containing Lercanidipine HCL. Optimized liquid SNEDDS formulation showed 96.19 % of drug diffusion with 50 nm droplet size, -23.2 mV Zeta potential and had infinite dilution capability. In vitro drug diffusion of the optimized batch was highly dependent on selected independent variables with statistical significance (p <0.05).

Based on the solubility of Cinacalcet HCL in the combination of oil, surfactant and co surfactant Capmul MCM, Polysorbate 80 and PEG 400 were selected, respectively for the development of liquid SNEDDS formulation. The optimum formulation showed better drug diffusion 97.18 % with required droplet size 13.4 nm and Zeta potential -25.42 mV having infinite dilution capability. In vitro drug diffusion of the optimized batch was highly dependent on selected independent variables with statistical significance (p <0.05).

SNEDDS of Lercanidipine HCL and Cinacalcet HCL showed better diffusion of drug in comparison to the orally administered marketed formulation Lerka and Pth Tablet respectively. Thus, it was concluded from the research that the developed SNEDDS have better potential of efficacious treatments with reduction of dose and dosing frequency for
their administration by oral route with less side effects and more cost-effective as well acceptable to patients because of convenience of application.

5.6 References


