CHAPTER 5

SUMMARY AND CONCLUSION

Candesartan cilexetil is a prodrug which comes under BCS class II category. It is insoluble in water and has only 15% oral bioavailability. These properties made CC an ideal candidate for formulating into solid lipid microparticles.

The current study was aimed to develop controlled release solid lipid microparticles using stearic acid, carnauba wax, hydrogenated castor oil and cetostearyl alcohol, which was further formulated into controlled release compressed tablets and floating tablets. Further, new analytical methods were developed and validated to determine the drug content and in vitro drug release profile.

Preformulation studies were carried out to develop RP-HPLC methods for estimation of CC, and to investigate any drug polymer interactions. The simple, sensitive and inexpensive isocratic RP-HPLC methods were developed and validated as per ICH guidelines. Validated parameters proved that the developed methods were very precise, linear, rugged and highly robust. Drug polymer interactions studies were carried out using FTIR and DSC analysis, which confirmed that there were no interactions between the drug and selected excipients. The nature and morphology of CC were characterized by XRD and SEM analysis, which explored that CC was crystalline in nature and irregular needle in shape.
In the present study, a total of twelve formulations of SLM of CC were prepared by fusion method. The formulations SLM-1 to SLM-4 were prepared with 1:1 ratio of drug and lipophilic excipients, SLM-5 to SLM-8 were prepared with 1:3 ratio and SLM-9 to SLM-12 were developed with the intermediate drug polymer ratio of 1:2. The estimated drug content from the prepared SLM indicated that all the prepared formulations contained favourable drug content. Among all twelve formulations, the formulations made with the ratio of 1:2 (SLM-9 to SLM-12) showed maximum and linear drug release. These four formulations were further subjected into FTIR, DSC, XRD and SEM analysis. The FTIR studies indicated that there was no interaction between the drug and polymers. The DSC and XRD studies indicated that there was a change in nature from crystalline to amorphous and SEM indicated that there was a reduction in the particle size. Overall, these studies indicated that the prepared SLM maintained the purity and integrity of the drug.

The prepared formulations of SLM were used to make compressed tablets by direct compression method. The prepared SLM were mixed with other excipients such as soluble diluent lactose and lubricants to make the blend for compressed tablets. The physicochemical parameters such as LOD, compressibility index, Hausner ratio and angle of repose were determined for the prepared blends. All the results of physicochemical parameters were observed within the specified limit. This indicated that all the prepared granules showed good flow properties thus, it may help in the compression of tablets without any defects.

The prepared blends were compressed as tablets and the tablets were evaluated for physicochemical and in vitro release studies. All the compressed controlled release formulations of CC showed almost uniform mass, thickness and drug content, and also exhibited excellent mechanical
strength. The in vitro release studies of compressed tablets of CC showed that the formulations prepared with cetostearyl alcohol showed maximum drug release in a controlled release manner compared to all other formulations prepared with hydrogenated castor oil, stearic acid and carnauba wax. Furthermore, optimum and linear in vitro release was observed in the formulations made with 1:2 ratio of drug and lipophilic excipients (F9 to F12). These four formulations were selected for further release kinetics and accelerated stability studies. Co-efficient of determination ($R^2$) was used to evaluate the accuracy of fit. All the selected formulations showed best fit to Higuchi model. According to this model the drug release from the compressed tablets was controlled by diffusion through the micropores. The formulations F9, F10 and F12 followed first order kinetics, which were concentration dependent whereas, F11 followed zero order kinetics and the drug release mechanism was followed independent of concentration.

The accelerated stability study data of selected formulations of compressed tablets of CC showed that there were no significant changes observed in the drug content and in vitro drug release during and at the end of the accelerated stability studies. The tested tablets also exhibited satisfactory appearance, thickness, weight variation and hardness during and at the end of the accelerated study period.

Eight formulations of controlled release floating tablets of CC were formulated using SLM. The SLM were prepared with 1:1 and 1:1.5 ratios of drug and lipophilic excipients such as cetostearyl alcohol, hydrogenated castor oil, stearic acid and carnauba wax. The formulations F1 to F4 contains SLM made with 1:1 ratio of drug and lipophilic excipients and F5 to F8 enclosed SLM made with 1:1.5 ratio. The prepared SLM were mixed with other excipients such as ethylcellulose, lactose and Povidone K-30 by direct compression method. Sodium bicarbonate and citric acid were used as gas
generating agents, magnesium stearate and talc were used as lubricants to make the blends for controlled release floating tablets. The prepared blends physicochemical parameters were evaluated by performing LOD, compressibility index, Hausner ratio and angle of repose. The results of different physicochemical parameters of floating tablet granules of CC were observed within the specified limit thus, demonstrated that all the prepared granules showed good to fair flow properties, which may help in the compression of tablets without any defects.

The prepared blends were further compressed into tablets and evaluated for weight variation, thickness, hardness, friability, drug content, tablets density, swelling index, in vitro buoyancy and in vitro release. Physicochemical parameters such as weight variation, thickness, friability, hardness, tablets density and drug contents results were well within the pharmacopoeial limit and indicated that the prepared tablets have enough strength and required labelled amount of active drug. Formulations have higher concentration of ethylcellulose showed more hardness and proved the rate controlling polymer additionally increased binding efficiency of the formulations.

The swelling indices increased in the following order, F1 < F3 < F2 < F6 < F4 < F7 < F5 and F8. The formulations with higher concentration of ethylcellulose (F4, F5, F6, F7 and F8) showed total floating time of > 24 h. The formulation F5 was made with cetostearyl alcohol showed the maximum and linear in vitro drug release in a controlled manner when compared to all other formulations. Based on the in vitro release, the formulation F5 was selected as the best formulation for further studies. The mechanism of drug release from the selected formulations showed best fit to Higuchi model. According to this, mechanism of drug release was controlled by diffusion from the micropores of the matrices. The calculated $R^2$ values for the
determination of release kinetics obeyed first-order and this demonstrated that the drug release was completely dependent on the concentration.

The accelerated stability studies data of selected formulation F5 revealed that there were no significant changes observed in the drug content during and at the end of the accelerated stability study. The tested tablets also exhibited satisfactory appearance, thickness, weight variation, hardness, friability, *in vitro* buoyancy and *in vitro* drug release during and at the end of the accelerated study period.

*In vitro* drug release profile of pure CC in phosphate buffer (pH 7.2) was compared with optimized formulation of compressed tablet of CC (F11) and floating tablets of CC (F5). The results showed higher and controlled release in the selected formulations. Hence, it is concluded that CC tablets formulated with lipophilic carriers had increased the drug dissolution and bioavailability with an addition of soluble excipient lactose. Furthermore, floating tablets composed of desirable concentrations of fatty alcohol, sodium bicarbonate, citric acid, ethylcellulose and lactose had enhanced the total floating time in the gastric medium thereby increased the bioavailability.

Improved gastrointestinal absorption by improving the solubility, reducing the dose size and dosing frequency of CC was achieved by developing SLM using lipids such as fatty alcohol, fatty acid, polar wax and hydrogenated castor oil. Furthermore, in this study new RP-HPLC methods for assay and dissolution were developed and validated. From the study it is confirmed that the formulations containing desirable ratio of cetostearyl alcohol with other additives showed effective control and maximum *in vitro* release. Thus, concluded that solid lipid microparticles containing compressed tablets and floating tablets of CC with improved dissolution for once daily administration were successfully prepared with considerable good stability. Therefore, the two main issues such as, the untoward effects and patient
non-compliance associated with the management of high blood pressure is expected to be addressed with the developed controlled release formulations of Candesartan cilexetil.