6. SUMMARY AND CONCLUSIONS

Drug absorption from the gastro intestinal tract can be limited by various factors with the most common one being poor aqueous solubility and poor permeability of a drug molecule. When delivering an active ingredient orally, it must first dissolve in gastrointestinal fluids before it can then permeate the membranes of the gastro intestinal tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption. Solubility behaviour of a drug plays a key role for its oral bioavailability. For some drugs solubility presents a challenge to the development of a suitable formulation for oral administration. Therefore solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs. Screening methods for identifying potential drug candidates identified a number of poorly soluble drugs as potential therapeutic agents. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Many of the potential drugs are abandoned in the early stages of development due to solubility problems. Therefore it is more important that methods for overcoming solubility limitations should be identified and applied commercially such that potential therapeutic benefits of these agents can be realized.

Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach was fast dissolving tablets which have gained acceptance and popularity in the recent time. Several pharmaceutical industries prepared fast dissolving tablets by direct compression technique by selecting suitable super disintegrants. Direct compression technique offers important advantages such as increased output, reduced cost, less machinery and improved drug stability when compared to wet granulation method.

The aim of the work is to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble drugs lovastatin and simvastatin by formulating it as solid dispersions using
various techniques with PEG-6000 as a carrier and subsequent preparation of fast dissolving tablets with the prepared solid dispersions using different concentrations of super disintegrants and comparing them with that of the marketed product. Lovastatin is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidaemias and prevention of ischaemic heart disease. It is practically insoluble in water, sparingly soluble in alcohol and soluble in acetone.

Lovastatin is absorbed from the gastrointestinal tract and is hydrolysed in the liver to its active beta hydroxy form. Peak plasma concentration occurs within 2-4 hours. The half life of the active metabolite is 1 to 2 hours. Simvastatin is a lipid regulating drug. It is a competitive inhibitor of HMG-CoA used to reduce LDL-cholesterol, apolipoprotein B, and to increase HDL-cholesterol in the treatment of hyperlipidaemias, including hypercholesterolaemias, combined hyperlipidaemia, hypertriglyceridaemia and dysbetalipoproteinaemia. It is practically insoluble in water, freely soluble in alcohol and soluble in dichloromethane. Simvastatin is absorbed from the gastrointestinal tract and is hydrolysed to its beta hydroxy form. The half-life of the active beta hydroxyacid metabolite is 1.9 hours.

Based on their physicochemical and biopharmaceutical properties, Lovastatin and Simvastatin were selected as a drug candidates for developing solid dispersion formulations for improving its solubility and bioavailability by improving the dissolution rate.

In the present investigation lovastatin and simvastatin solid dispersion were prepared by physical mixing, fusion, solvent evaporation and lyophilization methods using polyethylene glycol-6000 as an inert amphiphilic carrier. The prepared solid dispersions were evaluated for pre compressional parameters such as angle of repose, carr’s index, particle size and drug content. Further in vitro dissolution studies were performed on all the prepared solid dispersions by using USP type II dissolution apparatus with 900ml pH 7.0 phosphate buffer
maintained at 37±0.5°C with a paddle speed 50 rpm. The dissolution parameters such as \( T_{30} \), \( T_{90} \), \( \text{DE}_{20\%} \), \( K \), \( R^2 \) were calculated for all the solid dispersions. The pure drug Lovastatin and Simvastatin along with optimized solid dispersions were characterised by DSC, PXRD, SEM analysis.

The lovastatin and simvastatin optimized solid dispersions which shows better dissolution rate were then formulated as fast dissolving tablets by using newer super disintegrants such as pregelatinised starch, sodium starch glycolate, croscarmellose sodium, crospovidone. All the tablet formulations were evaluated for physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion time and drug content as per the IP specifications. All the batches of tablet formulations were subjected to in vitro dissolution studies as per the earlier stated method for solid dispersions. All the dissolution parameters such as \( T_{30} \), \( T_{90} \), \( \text{DE}_{20\%} \), \( K \), \( R^2 \) were calculated for all the tablet formulations. Based on the in vitro dissolution studies optimized fast dissolving tablets of lovastatin and simvastatin which showed dissolution were further subjected to in vivo pharmacokinetic studies.

In vivo pharmacokinetic studies for the optimized fast dissolving tablets of lovastatin and simvastatin were calculated in albino rabbits. The tablet formulations were dispersed in distilled water and fed to different rabbit groups through oral route by using soft oral tube. The blood samples were withdrawn from the rabbits at various time intervals and plasma was separated. The plasma drug concentrations were estimated by using HPLC method. The amount of drug available in plasma versus time plots were drawn and the pharmacokinetic parameters such as \( C_{\text{max}} \), \( T_{\text{max}} \), \( T_{\frac{1}{2}} \), \( \text{AUC}_{(0-t)} \), \( \text{AUMC}_{(0-t)} \), MRT were calculated by using PK summit solutions software USA.

The fast dissolving tablets of lovastatin and simvastatin subjected to in vivo pharmacokinetic studies were also tested for accelerated stability studies. These tablets were
stored at 25±2°C, 60±5% RH for 6 months and 40±2°C, 75±5% RH for 3 months. Then samples of tablet formulation were further evaluated for physical parameters as described earlier. Further these were subjected to in vitro dissolution studies.

**Based on the investigations performed the following conclusions were drawn:**

1. Based upon the physicochemical and biopharmaceutical characteristics the drugs selected such as lovastatin and simvastatin were found to be suitable candidates for preparation of solid dispersions for improving their solubility and bioavailability by improving the dissolution rate.

2. Saturated solubility studies were performed on lovastatin and simvastatin, were found to exhibit high solubility in pH 7.0 phosphate buffer. Hence pH 7.0 phosphate buffer was selected as a dissolution media for further studies.

3. Solid dispersions of lovastatin and simvastatin were prepared by physical mixing, fusion, solvent evaporation and lyophilisation methods and found to be stable, discrete particulate form with free flowing characteristics.

4. All the solid dispersions prepared by various methods were found to be stable and exhibited good flow properties. The angle of repose values obtained for various solid dispersions were in the range of 19.56° to 24.28° which indicated the good flow properties of dispersions.

5. The Carr's index values obtained for various solid dispersions were in the range of 14.17 to 15.52% which indicated the good flow properties of dispersions.

6. The average particle size for all the solid dispersions were in the range of 173-178 µm.
7. The drug content for all the dispersions were in the range of 9.56 to 10.15 mg of Lovastatin and Simvastatin respectively.

8. Lovastatin solid dispersions prepared by physical mixing, fusion, solvent evaporation and lyophilization methods were found to release the drug by increasing the dissolution rate upto 1.20 to 3.59 folds than compared to pure drug dissolution.

9. Lovastatin solid dispersions were found to follow the first order kinetics with $R^2$ values in the range of 0.9632 to 0.9938 obtained for all the solid dispersions and they were found to be linear.

10. Based on the in vitro dissolution studies solid dispersions LS12 and LL16 prepared by solvent evaporation and lyophilization methods were found to exhibit high dissolution rate than compared to the others and hence these two dispersions were further selected for preparation of fast dissolving tablets by using newer super disintegrants.

11. Simvastatin solid dispersions prepared by physical mixing, fusion, solvent evaporation and lyophilization methods were found to release the drug by increasing the dissolution rate upto 1.20 to 2.97 folds than compared to pure drug dissolution.

12. Simvastatin solid dispersions were found to follow the first order kinetics with $R^2$ values in the range of 0.9060 to 0.9821 and they were found to be linear.

13. The order of increased dissolution rate for various solid dispersions prepared by different methods were lyophilization > solvent evaporation > physical mixing for all the solid dispersions of lovastatin and simvastatin.

14. Based on the in vitro dissolution studies solid dispersions SS12 and SL16 prepared by solvent evaporation and lyophilization methods were found to exhibit high dissolution
rate than compared to others and hence these two dispersions were further selected for preparation of fast dissolving tablets by using newer super disintegrants.

15. DSC thermogram of lovastatin exhibited a sharp peak at 173.4°C; polyethylene glycol-6000 exhibited a peak at 67.9°C, while lovastatin solid dispersion (LL16) showed that there was no sharp endothermic peak at 173.4°C indicating no physical interaction between lovastatin and polyethylene glycol-6000.

16. PXRD diffraction pattern of pure drug lovastatin shows a highly crystalline nature, polyethylene glycol-6000 at 2θ angle showed less peaks while of lovastatin solid dispersions showed a significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks.

17. SEM photomicrographs of pure lovastatin showed characteristic needle shaped crystals while lovastatin solid dispersions prepared by solvent evaporation observed as amorphous form of the dispersion and lyophilization method showed that dispersion was highly porous, loosely networked, friable and low dense form.

18. DSC thermogram of simvastatin exhibited a sharp peak at 141.8°C, polyethylene glycol-6000 exhibited 67.9°C while solid dispersion (SL16) showed no sharp endothermic peak at 141.8°C indicated no physical interaction between Simvastatin and polyethylene glycol-6000.

19. PXRD diffraction pattern of pure drug simvastatin showed a highly crystalline nature, indicated by numerous distinctive peaks and PXRD pattern of polyethylene glycol-6000 showed less peaks while PXRD pattern of simvastatin solid dispersions showed significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks.
20. SEM photomicrographs of pure simvastatin showed characteristic needle shaped crystals observed while solid dispersions prepared by solvent evaporation observed as amorphous form of the dispersion. Solid dispersions prepared by lyophilization method showed that dispersion was highly porous, loosely networked, friable and low dense form.

21. The optimised solid dispersions LS12, LL16 of lovastatin and SS12, SL16 of simvastatin were further formulated as fast dissolving tablets by using various proportions of sodium starch glycolate, pregelatinised starch, crospovidone and croscarmellose sodium as super disintegrants.

22. All the formulations prepared were found to be stable and meeting IP specified limits for weight uniformity, friability, dispersion time and drug content.

23. It was observed that all the lovastatin fast dissolving tablets were found to follow the first order kinetics with $R^2$ values in the range of 0.9313 to 0.9973 and were found to be linear.

24. The order of release of drug from fast dissolving tablets with various super disintegrants were CCS > CP > SSG > PGS.

25. Based on the in vitro dissolution studies of fast dissolving tablets LT 13 and LT 26 prepared by CCS as super disintegrant were found to exhibit high dissolution rate than compared to the others and hence these two tablets were further selected for in vivo and accelerated stability studies as per ICH guidelines.

26. It was observed that all the simvastatin fast dissolving tablets were found to follow the first order kinetics with $R^2$ values in the range of 0.9573 to 0.9932 and were found to be linear.
27. Based on the *in vitro* dissolution studies of fast dissolving tablets LT13 and LT26 prepared by CCS as super disintegrant was found to exhibit high dissolution rate compared to others and hence these two tablets were further selected for *in vivo* and accelerated stability studies as per ICH guidelines.

28. The dissolution studies indicated that fast dissolving tablets LT13 and LT26 gave improved dissolution characteristics of Lovastatin than that of the marketed tablet. All the tablet formulations including marketed tablet were found to comply with the IP acceptance limits of dissolution testing.

29. The dissolution studies indicated that the fast dissolving tablets ST13 and ST26 gave improved dissolution characteristics of lovastatin than that of the marketed tablet. All the tablet formulations including marketed tablet were found to comply with the IP acceptance limits of dissolution testing.

30. The *in vivo* pharmacokinetic studies indicated that fast dissolving tablets LT13 and LT26 exhibited improved lovastatin plasma concentrations by extending the mean residence time upto 6.9 and 6.6 hrs while the oral solution extended upto 5.5 hrs with increased AUC values of 183 ng-hr/ml and 165 ng-hr/ml while that of oral solution having the AUC of 123 ng-hr/ml resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

31. The invivo pharmacokinetic studies indicated that fast dissolving tablets ST13 and ST26 exhibited improved simvastatin plasma concentrations by extending the mean residence time 2.9 and 2.7 hrs while the oral solution upto 2.7 hrs, with increased AUC values of 107 ng-hr/ml and 110 ng-hr/ml while the oral solution with AUC of 71 ng-hr/ml resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.
Accelerated stability studies indicated that there were no visible physical changes observed in the tablets after storage. It was also observed that there was no significant change in the drug release patterns from these tablets. Based on these accelerated stability studies it was concluded that tablet formulations LT13, LT26 of lovastatin and ST13, ST26 of simvastatin were found to be quite stable.

**RECOMMENDATIONS**

The results of the present investigation clearly indicated that the preparation of solid dispersions by physical mixing, fusion, solvent evaporation and lyophilization methods greatly improved the solubility and dissolution rate of poorly soluble drugs, lovastatin and simvastatin. PEG 6000 used as an inert amphilic carrier was found suitable for the preparation of solid dispersions by various methods. It was observed that as the proportion of PEG concentration increased the solubility and dissolution characteristics were improved for the solid dispersions. All the solid dispersions exhibited good flow characteristics with uniform particle size. Among the various methods of preparation of solid dispersions, lyophilization method was found to the best method. The solid dispersion were further formulated as fast dissolving tablets by using newer super disintegrants and were found to comply with the Indian pharmacopoeial specifications. Among the newer super disintegrants crosscarmellose sodium was found to be suitable super disintegrant to enhance the rapid wettabiliy and dispersion of the tablets and thus improved the rate of dissolution. The other objectives of the investigation such has *in vivo* pharmacokinetic studies showed improved bioavailability of these formulations and accelerated stability studies indicated the stability of fast dissolving tablets. Thus the main aim and objective of the present investigation was fulfilled and achieved.