Drug absorption from the gastrointestinal 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 gastrointestinal 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 Atorvastatin Calcium and Rosuvastatin Calcium by formulating them 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.

Atorvastatin Calcium is a HMG-CoA reductase inhibitor used in the treatment of dyslipidemia and prevention of cardiovascular disease. It is very slightly soluble in water, slightly soluble in ethanol and freely soluble in methanol. Atorvastatin Calcium is rapidly absorbed after oral administration with absolute bioavailability of parent drug is approximately 12% and is hydrolysed in the liver to ortho and para hydroxylated derivatives. Peak plasma concentrations achieved with in 1-2hours. The half life is 14 hours.

Rosuvastatin is a lipid regulating drug, it is a competitive inhibitor of HMG-CoA used to reduce cholesterol, used in the
treatment of osteoporosis, benign prostatic hyperplasia, dysbetalipoproteinemia and alzheimer's disease. It is sparingly soluble in water, ethanol and soluble in methanol. Rosuvastatin Calcium is absorbed from the gastrointestinal tract and is metabolised in the liver. Peak plasma concentrations achieved with in 3-5 hours. The half life is 19 hours.

Based on their physicochemical and biopharmaceutical properties, Atorvastatin Calcium and Rosuvastatin Calcium 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 Atorvastatin Calcium and Rosuvastatin Calcium solid dispersion were prepared by physical mixing, fusion, solvent evaporation and lyophilisation methods using polyethylene glycol-6000 as an inert amphiphilc 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 6.8 phosphate buffer maintained at 37±0.5° C with a paddle speed 50 rpm. The dissolution parameters such as T₅₀, T₉₀, DE₂₀%, K, R² were calculated for all the solid dispersions. The pure drug Atorvastatin Calcium and Rosuvastatin Calcium along with
optimized solid dispersions were characterised by DSC, PXRD, SEM analysis.

The Atorvastatin Calcium and Rosuvastatin Calcium optimized solid dispersions which shows better dissolution rate were then formulated as fast dissolving tablets by using newer superdisintegrants 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 $T_{50}$, $T_{90}$, $DE_{20\%}$, $K$, $R^2$ were calculated for all the tablet formulations. Based on the in vitro dissolution studies optimized fast dissolving tablets of Atorvastatin Calcium and Rosuvastatin Calcium which showed dissolution were further subjected to in vivo pharmacokinetic studies.

In vivo pharmacokinetic studies for the optimized fast dissolving tablets of Atorvastatin Calcium and Rosuvastatin Calcium 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 $C_{\text{max}}$, $T_{\text{max}}$, $T_{\frac{1}{2}}$, AUC$_{(0-t)}$, AUMC$_{(0-t)}$, MRT were calculated by using PK summit solutions software USA.

The fast dissolving tablets of Atorvastatin Calcium and Rosuvastatin Calcium subjected to in vivo pharmacokinetic studies were also tested for accelerated stability studies. These tablets were stored at $25\pm 2^0C$, $60\pm 5\%$ RH for 6 months and $40\pm 2^0C$, $75\pm 5\%$ 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 Atorvastatin Calcium and Rosuvastatin Calcium 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 Atorvastatin Calcium and Rosuvastatin Calcium, were found to exhibit high solubility in pH 6.8 phosphate buffer. Hence pH 6.8 phosphate buffer was selected as a dissolution media for further studies.
3. Solid dispersions of Atorvastatin Calcium and Rosuvastatin Calcium 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 16.96° to 24.65° which indicated the excellent flow properties of dispersions.

5. The Carr's index values obtained for various solid dispersions were in the range of 12.97 to 15.96% which indicated the excellent flow properties of dispersions.

6. The average particle size for all the solid dispersions were in the range of 171-179 μm.

7. The drug content for all the dispersions were in the range of 19.41 to 20.05 mg of Atorvastatin Calcium and Rosuvastatin Calcium respectively.

8. Atorvastatin Calcium solid dispersions prepared by physical mixing, fusion, solvent evaporation and lyophilisation methods were found to release the drug by increasing the dissolution rate upto 1.12 to 2.59 folds than compared to pure drug dissolution.

9. Atorvastatin Calcium solid dispersions were found to follow the first order kinetics with R^2 values in the range of 0.9735 to 0.9933
obtained for all the solid dispersions and they were found to be linear.

10. Based on the *in vitro* dissolution studies solid dispersions AF 8 and AL 16 prepared by fusion and lyophilisation 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. Rosuvastatin Calcium solid dispersions prepared by physical mixing, fusion, solvent evaporation and lyophilisation methods were found to release the drug by increasing the dissolution rate upto 1.57 to 2.25 folds than compared to pure drug dissolution.

12. Rosuvastatin Calcium solid dispersions were found to follow the first order kinetics with \( R^2 \) values in the range of 0.9060 to 0.9821and they were found to be linear.

13. The order of increased dissolution rate for various solid dispersions prepared by different methods were lyophilisation > fusion > solvent evaporation > physical mixing for all the solid dispersions of Atorvastatin Calcium and Rosuvastatin Calcium.

14. Based on the *in vitro* dissolution studies solid dispersions RF 8 and RL16 prepared by fusion and lyophilisation 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 Atorvastatin Calcium exhibited a sharp peak at 232.7°C; polyethylene glycol-6000 exhibited a peak at 66.4°C, while Atorvastatin Calcium solid dispersion (AF 8) it was observed that there was endothermic peak at 241.8°C. In the DSC thermogram of Atorvastatin Calcium solid dispersion (AL 16) it was observed that there was endothermic peak at 218.9°C. From the spectra it was observed that a little change in melting isotherm which may be due to partial change in the crystallinity. It is indicated that the drug is incorporated in the polymer and their was no interaction between drug and polymer.

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

17. FTIR spectra of both the solid dispersions prepared by fusion and Lyophilisation methods showed a peak of the amide C=O stretch vibration of the Atorvastatin Calcium. The result suggested that there was no interaction between Atorvastatin Calcium and PEG-6000 in their combinations.
18. SEM photomicrographs of pure Atorvastatin Calcium showed characteristic needle shaped crystals while Atorvastatin Calcium solid dispersions prepared by fusion observed as amorphous form of the dispersion and lyophilisation method showed that dispersion was highly porous, loosely networked, friable and low dense form.

19. DSC thermogram of Rosuvastatin Calcium exhibited a sharp peak at 231.2°C, polyethylene glycol-6000 exhibited 66.4°C, while Rosuvastatin Calcium solid dispersion (RF 8) it was observed that there was endothermic peak at 238.5°C. In the DSC thermogram of Rosuvastatin Calcium solid dispersion (RL 16) it was observed that there was endothermic peak at 223.1°C. From the spectra it was observed that a little change in melting isotherm which may be due to partial change in the crystallinity. It is indicated that the drug is incorporated in the polymer and there was no interaction between drug and polymer.

20. PXRD diffraction pattern of pure drug Rosuvastatin Calcium showed a highly crystalline nature, indicated by numerous distinctive peaks and PXRD pattern of polyethylene glycol-6000 showed less peaks while PXRD pattern of Rosuvastatin Calcium solid dispersions showed significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks.

21. FTIR spectra of of both the solid dispersions prepared by fusion and Lyophilisation methods showed a peak of the carboxylic O-H stretch vibration of the Rosuvastatin Calcium. The result suggested
that there was no interaction between Rosuvastatin Calcium and PEG-6000 in their combinations.

22. SEM photomicrographs of pure Rosuvastatin Calcium showed characteristic needle shaped crystals observed while solid dispersions prepared by fusion observed as amorphous form of the dispersion. Solid dispersions prepared by lyophilisation method showed that dispersion was highly porous, loosely networked, friable and low dense form.

23. The optimised solid dispersions AF 8, AL 16 of Atorvastatin Calcium and RF 8, RL 16 of Rosuvastatin Calcium were further formulated as fast dissolving tablets by using various proportions of sodium starch glycolate, pregelatinised starch, crospovidone and croscarmellose sodium as super disintegrants.

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

25. It was observed that all the Atorvastatin Calcium fast dissolving tablets were found to follow the first order kinetics with $R^2$ values in the range of 0.9833 to 0.9993 and were found to be linear.

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

27. Based on the in vitro dissolution studies of fast dissolving tablets AT 13 and AT 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.

28. It was observed that all the Rosuvastatin Calcium fast dissolving tablets were found to follow the first order kinetics with $R^2$ values in the range of 0.9856 to 0.9980 and were found to be linear.

29. Based on the *in vitro* dissolution studies of fast dissolving tablets RT 13 and RT 26 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.

30. The dissolution studies indicated that fast dissolving tablets AT 13 and AT 26 gave improved dissolution characteristics of Atorvastatin Calcium 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.

31. The dissolution studies indicated that the fast dissolving tablets RT 13 and RT 26 gave improved dissolution characteristics of Rosuvastatin Calcium 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.

32. The *in vivo* pharmacokinetic studies indicated that fast dissolving tablets AT 13 and AT 26 exhibited improved Atorvastatin Calcium
plasma concentrations by extending the mean residence time upto 733.2 min and 762.6 min while the oral solution extended upto 675.2 min with increased AUC values of 283039 ng-hr/ml and 293894 ng-hr/ml while that of oral solution having the AUC of 184342 ng-min/ml resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

33. The *in vivo* pharmacokinetic studies indicated that fast dissolving tablets RT 13 and RT 26 exhibited improved Rosuvastatin Calcium plasma concentrations by extending the mean residence time 766.0 min and 847.3 min while the oral solution upto 747.3 min, with increased AUC values of 422460 ng-hr/ml and 435821 ng-hr/ml while the oral solution with AUC of 220140 ng-min/ml resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

34. 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 AT 13, AT 26 of Atorvastatin Calcium and RT 13, RT 26 of Rosuvastatin Calcium 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 Lyophilisation methods greatly improved the solubility and dissolution rate of poorly soluble drugs, Atorvastatin calcium and Rosuvastatin Calcium. 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-6000 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, lyophilisation method was found to the best method. The solid dispersion were further formulated as fast dissolving tablets by using newer superdisintegants 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. Hence it is recomended that the lyophilisation method was found to be suitable for enhancing solubility and dissolution rate of poorly soluble drugs
with PEG-6000 as carrier and croscarmellose sodium can be as superdisintegrant used to prepare fast dissolving tablets.