5. DISCUSSION OF RESULTS

An increased demand for more patient friendly dosage forms has been observed since past few years. The oral route of drug administration is the most preferred method of delivery due to convenience and ease of ingestion. From a patient’s perspective swallowing a dosage form is a comfortable and a familiar means of taking medication. Although oral route of administration is preferred for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption results in poor bioavailability and is most common among the problems that can be encountered when delivering an active agent via oral route. 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.

The present research work has been carried out with an aim to increase the solubility and dissolution rate of lovastatin and simvastatin, further optimized solid dispersions were formulated as fast dissolving tablets with super disintegrants to improve the wettability and dispersion time as well as to reduce disintegration time and finally to improve the drug release characteristics for enhancing the bioavailability.

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 with in 2-4 hours. The half life of the active metabolite is 1 to 2 hours. (Modi, 2007)

Simvastatin is a lipid regulating drug. It is a competitive inhibitor of HMG-CoA used to reduce LDL-cholesterol, apo lipoprotein 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. (Pinnamneni, 2002)

Based on the above physical, chemical, biopharmaceutical properties and clinical relevance, 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.

5.1. Lovastatin and Simvastatin analysis

Lovastatin and simvastatin were analysed by simple, sensitive UV spectrophotometric methods. Lovastatin and simvastatin were dissolved in methanol and then from the methanolic stock solutions standard dilutions were made with pH 7.0 phosphate buffer. Lovastatin was estimated at wave length 238 nm by using pH 7.0 phosphate buffer as blank. (Mehardad, 2009) Simvastatin was estimated at wave length 239 nm by using pH 7.0 phosphate buffer as blank. (Balaji, 2010) These methods were adopted for estimation of drugs in the solid dispersions and also in in vitro dissolution studies. Lovastatin was estimated in the concentration range of 2-10 µg/ml. Simvastatin was estimated in the concentration range of 2-10 µg/ml. Both the analytical methods were linear in the concentration range and obeys the Beers law. The estimation methods were found to be simple, sensitive and reproducible for analysing Lovastatin and Simvastatin in pure form and in formulations. The calibration
In vivo pharmacokinetic studies of lovastatin and simvastatin were carried in rabbits. The Lovastatin and Simvastatin concentration in the rabbit plasma was estimated by HPLC method. (Islam Ulah, 2010) These methods were found to be suitable for determining the plasma concentration of drugs. The calibration curves for the estimation of Lovastatin and Simvastatin in the rabbit plasma were given in tables 4.3 and 4.4 and shown in figures 4.3 and 4.4.

5.2. Saturated Solubility Studies

Saturated solubility studies were performed on Lovastatin and Simvastatin by using different dissolution media. These studies were performed in a orbital shaker at 37°C with 50rpm for 24 hrs. (Srinivas, 2008) The solubility of Lovastatin and Simvastatin in different dissolution media were given in tables 4.5 and 4.6. Both the drugs 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. It was also observed that pH 7.0 phosphate buffer is the official dissolution medium specified in USP for both the drugs.

5.3. Preparation of Solid Dispersions of Lovastatin and Simvastatin

Solid dispersions of lovastatin and simvastatin were prepared by physical mixing, fusion, and solvent evaporation and lyophilisation methods by using polyethylene glycol-6000 as a carrier. The solid dispersions were prepared by changing the drug to polymer ratios. The compositions of various solid dispersions prepared by different methods were given in tables 4.7 & 4.8. All the solid dispersions were prepared under similar conditions to avoid processing variables. The solid dispersions were found to be stable, discrete particulate form
with free flowing characteristics. These were further evaluated for physical parameters such as angle of repose, carr's index, average particle size and drug content. (Balaji, 2011)

All the solid dispersions prepared by various methods were evaluated for angle of repose, carr's index, average particle size and drug content. It was found that all the solid dispersions were found to be stable and thus exhibited good flow properties. The angle of repose values obtained for various solid dispersions were in the range of $19.56^\circ$ to $24.28^\circ$ which indicated good flow properties of dispersions. The Carr's index values obtained for various solid dispersions were in the range of 14.17 to 15.52% which indicated good flow properties of dispersions. The pure drug form of lovastatin and simvastatin showed angle of repose values $30.28^\circ$ and $29.65^\circ$ and Carr's index values 18.52 and 18.75% respectively indicating the poor flow characteristics. The average particle size for all the solid dispersions were in the range of 173-178 µm. The drug content for all the dispersions were in the range of 9.56 to 10.15 mg. Thus all the solid dispersions were found to stable and suitable for compression as tablets. The physical parameters of Lovastatin and Simvastatin solid dispersions were given in tables 4.9 and 4.10.

5.4.Dissolution Studies of Lovastatin and Simvastatin Solid Dispersions

Dissolution studies were performed on the prepared solid dispersions of lovastatin and Simvastatin by using 8 station USP Type II dissolution apparatus with 900 ml of pH 7.0 phosphate buffer maintaining at $37\pm0.5^\circ$C with a paddle speed at 50rpm. These studies were performed in triplicate for all the solid dispersions. The dissolution rate of drug from solid dispersions were compared with the pure drug lovastatin and simvastatin dissolution. These studies indicated that all the solid dispersions prepared by various methods were found to exhibit high solubility and dissolution rate than compared to their respective pure drug forms.
Lovastatin solid dispersions prepared by physical mixing method were found to release the drug from 32.45% to 43.32%. It was observed that the dissolution rate of lovastatin was increased by 1.20 to 1.60 folds. Lovastatin solid dispersions prepared by fusion method were found to release the drug from 45.83% to 72.42%. It was observed that the dissolution rate of Lovastatin was increased by 1.69 to 2.68 folds. Lovastatin solid dispersions prepared by solvent evaporation method were found to release the drug from 70.17% to 96.98%. It was observed that the dissolution rate of lovastatin was increased by 2.60 to 3.59 folds. Lovastatin solid dispersions prepared by lyophilization method were found to release the drug from 83.55% to 98.98%. It was observed that the dissolution rate of lovastatin was increased by 3.09 to 3.66 folds than compared to the pure drug lovastatin dissolution. The pure drug lovastatin exhibited the dissolution rate up to only 26.99% in the pH 7.0 phosphate buffer. The dissolution profiles of pure drug lovastatin and the prepared solid dispersions were given in the tables 4.11 to 4.14 and shown in the figures 4.5 to 4.8.

The first order plots were plotted by taking log% undissolved versus time (min). The slope obtained from the linear line was multiplied with 2.303 to get first order rate constant (K) for various formulations. It was observed that all the lovastatin solid dispersions were found to follow first order kinetics. The R² values obtained for all the solid dispersions were linear and obtained in the range of 0.9637 to 0.9938. The in vitro dissolution parameters such as T₅₀, T₉₀, DE₂₀% of all the lovastatin solid dispersions were calculated and given in table 4.19. The T₅₀, T₉₀, DE₂₀% values of LS12 dispersions were 5 min, 27.5 min, 73.57% respectively. The T₅₀, T₉₀, DE₂₀% values of LL16 dispersions were 4 min, 25 min, 74.56% respectively. It was observed that as the proportion of carrier polyethylene glycol-6000 is increased in the solid dispersions, the dissolution rate of solid dispersions was increased. Lovastatin solid dispersions LS12 and LL16 were found to exhibit high dissolution rate than compared to other solid dispersions. This was due to the formation of drug-carrier complex which
conceals the lipophillic nature of drug. Among the various methods employed for preparation of solid dispersions lyophilization method was found to be more suitable for intense complex formation between the drug and carrier. The order of increased dissolution rate for various solid dispersions prepared by different methods were lyophilization > solvent evaporation > physical mixing. Based on the in vitro dissolution studies solid dispersions LL12 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.

Simvastatin solid dispersions prepared by physical mixing method were found to release the drug from 40.07% to 53.14%. It was observed that the dissolution rate of Simvastatin was increased by 1.20 - 1.59 folds. Simvastatin solid dispersions prepared by fusion method were found to release the drug from 43.21% to 75.84%. It was observed that the dissolution rate of simvastatin was increased by 1.29 - 2.27 folds. Simvastatin solid dispersions prepared by solvent evaporation method were found to release the drug from 73.18% to 97.24%. It was observed that the dissolution rate of simvastatin was increased by 2.19 - 2.91 folds. Simvastatin solid dispersions prepared by lyophilization method were found to release the drug from 85.54% to 99.17%. It was observed that the dissolution rate of simvastatin was increased by 2.56 - 2.97 folds than compared to the pure drug simvastatin dissolution. The pure drug simvastatin exhibited the dissolution rate up to 33.37% in pH 7.0 phosphate buffer. The dissolution profiles of pure drug simvastatin and the prepared solid dispersions were given in the tables 4.15- 4.18 and shown in the figures 4.9- 4.12.

The first order plots were plotted by taking log% undissolved versus time (min). The slope obtained from the linear line was multiplied with 2.303 to get first order rate constant (K) for various formulations. It was observed that all the simvastatin solid dispersions were found to follow the first order kinetics. The $R^2$ values obtained for all the solid dispersions were linear
and obtained in the range of 0.9060 to 0.9821. The \textit{in vitro} dissolution parameters such as $T_{50}$, $T_{90}$, DE$_{20} \%$ of all the simvastatin solid dispersions were calculated and given in the tables 4.20. The $T_{50}$, $T_{90}$, DE$_{20} \%$ values of SS12 dispersions were 4 min, 26 min, 71.37\% respectively. The $T_{50}$, $T_{90}$, DE$_{20} \%$ values of SL16 dispersions were 4 min, 17.3 min, 74.07\% respectively. It was observed that as the proportion of carrier polyethylene glycol-6000 is increased in the solid dispersions, the dissolution rate of solid dispersions was increased. Simvastatin solid dispersions SS12 and SL16 were found to exhibit high dissolution rate than compared to other solid dispersions. This was due to the formation of drug-carrier complex which conceals the lipophillic nature of drug. Among the various methods employed for preparation of solid dispersions lyophilization method was found to be more suitable for intense complex formation between the drug and carrier. The order of increased dissolution rate for various solid dispersions prepared by different methods were lyophilization $>$ solvent evaporation $>$ physical mixing. Based on the \textit{in vitro} dissolution studies solid dispersions SL12 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.

\textbf{5.5. Characterization of Lovastatin and Simvastatin Solid Dispersions}

The complex formation, crystalline characteristics of the drug and surface characteristics of the drug were further characterised by DSC, PXRD, SEM analysis. The DSC studies were carried out on DSC (DSC60, Schimadzu). The DSC thermogram of Lovastatin exhibits a sharp peak at 173.4$\degree$C. The melting endotherm of polyethylene glycol-6000 is in the temperature range of 67.9 $\degree$C. In the DSC thermogram of Lovastatin solid dispersion (LL16) it was observed that there was no sharp endothermic peak at 173.4 $\degree$C indicate no physical interaction between Lovastatin and polyethylene glycol-6000. The DSC thermograms of pure Lovastatin, polyethylene glycol-6000 and Lovastatin solid dispersions were shown in figures.
The DSC thermogram of Lovastatin solid dispersion indicated the formation of drug-carrier complex.

The PXRD patterns of Lovastatin, polyethylene glycol and lovastatin solid dispersion (LL16) were traced employing X-ray diffractometer (Bruker AXS). The diffraction pattern of pure drug lovastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle $2\theta$ throughout the scan range. PXRD pattern of polyethylene glycol-6000 at $2\theta$ angle showed the less peaks. PXRD pattern of Lovastatin solid dispersions shows a significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks. Thus the PXRD of lovastatin solid dispersion (LL 16) indicated the amorphous form of lovastatin complexed in the carrier polyethylene glycol-6000. (Monica, 2011) The PXRD patterns of pure lovastatin, polyethylene glycol-6000 and lovastatin solid dispersions were shown in fig 4.24.

SEM photomicrographs that reveal the surface morphology of sample were taken by a scanning electron microscope (JSEM 6390). In the SEM photomicrographs of pure Lovastatin characteristic needle shaped crystals were observed. SEM photomicrographs of Lovastatin solid dispersions prepared by solvent evaporation were observed as amorphous form. SEM photomicrographs prepared by lyophilisation method showed that dispersion was highly porous, loosely networked, friable and low dense form. The SEM photomicrographs of pure Lovastatin, and Lovastatin solid dispersions (LS12, LL16) were shown in figures 4.25 to 4.27.

The DSC studies were carried out on DSC calorimeter (DSC60, Schimadzu). The DSC thermogram of Simvastatin exhibits a sharp peak at $141.8^\circ$C. The melting endotherm of polyethylene glycol-6000 is in the temperature range of $67.9^\circ$C. In the DSC thermogram of simvastatin solid dispersion (SL16) it was observed that there was no sharp endothermic peak.
at 141.8°C indicate no physical interaction between simvastatin and polyethylene glycol-6000. The DSC thermograms of pure simvastatin, polyethylene glycol-6000 and Simvastatin solid dispersions were shown in figures 4.28 to 4.30. The DSC thermogram of Simvastatin solid dispersion indicated the formation of drug-carrier complex.

The PXRD patterns of simvastatin, polyethylene glycol and simvastatin solid dispersion (SL16) were traced employing X-ray diffractometer (Bruker AXS). The diffraction pattern of pure drug simvastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle $\theta$ throughout the scan range. PXRD pattern of polyethylene glycol-6000 at $\theta$ angle showed the less peaks. PXRD pattern of simvastatin solid dispersions shows a significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks. Thus the PXRD of simvastatin solid dispersion (LL 16) indicated the amorphous form of simvastatin complexed in the carrier polyethylene glycol-6000. The PXRD patterns of pure Simvastatin, polyethylene glycol-6000 and simvastatin solid dispersions were shown in fig 4.31.

SEM photomicrographs that reveal the surface morphology of sample were taken by a scanning electron microscope (JSEM 6390). In the SEM photomicrographs of pure Simvastatin characteristic needle shaped crystals were observed. SEM photomicrographs of Simvastatin solid dispersions prepared by solvent evaporation observed as amorphous form of the dispersion. SEM photomicrographs prepared by lyophilisation method showed that dispersion was highly porous, loosely networked, friable and low dense form. (Anshuman, 2005) The SEM photomicrographs of pure Simvastatin, and Simvastatin solid dispersions (SS12, SL16) were shown in figures 4.32 to 4.34.
5.6. Preparation of Fast Dissolving Tablets of Lovastatin and Simvastatin

The optimised solid dispersions LS12, LL 6 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. The super disintegrant proportion in various tablet formulations were taken at 1.25, 2.5, 5% w/w of the total tablet weight. The tablets were prepared by direct compression method using Clit 10 station mini press. All the batches of tablets were compressed under similar conditions to avoid processing variables. (Rakesh, 2008) The composition of various tablet formulations of Lovastatin and Simvastatin were give in tables 4.21 to 4.24. Further these tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion time and drug content for checking the stability of tablets. These studies reveal that the entire tablet formulations were stable meeting IP specified limits. The hardness of the tablets was in the range of 3.5 kg/cm$^2$. The uniformity of weight of different batches of tablets was in the range of 197-205 mg. The friability of different batches of tablets was in the range of 0.16-0.28%. The wetting time of different batches of tablets was in the range of 53-71 sec. The dispersion times of different batches of tablets were in the range of 58-182 sec. Drug content in the different batches of tablets were in the range of 9.56-10.10 mg. The physical parameters of various lovastatin and simvastatin fast dissolving tablets were given in the tables 4.25-4.28.

5.7. Dissolution Studies of Fast Dissolving Tablets of Lovastatin

Dissolution studies were performed on the prepared fast dissolving tablets of lovastatin by using 8 station USP Type II dissolution apparatus with 900 ml of pH 7.0 phosphate buffer maintaining at 37±0.5°C with a paddle speed at 50rpm. These studies were performed in triplicate for all the tablets. The dissolution rate of drug from tablets prepared with various
super disintegrants was compared with the tablet prepared without the super disintegrant. These studies indicated that all the tablet formulations prepared by using various super disintegrants were found to exhibit high dissolution rate than compared to the tablet prepared without super disintegrant. It was found that the tablets prepared by using the lyophilised dispersions were found to release the drug at a faster rate when compared to the tablets prepared by using dispersions of solvent evaporation. The dissolution profiles of lovastatin fast dissolving tablets were given in the tables 4.29 to 4.36 and shown in the figures 4.35 to 4.42.

The first order plots were plotted by taking log % undissolved versus time (min). The slope obtained from the linear line was multiplied with 2.303 to get first order rate constant (K) for various formulations. It was observed that all the lovastatin fast dissolving tablets were found to follow the first order kinetics. The $R^2$ values obtained for all the tablets were linear and obtained in the range of 0.9313 to 0.9973. The *in vitro* dissolution parameters such as $T_{50}$, $T_{90}$, DE$_{20}^{\%}$ for all the lovastatin fast dissolving tablets were calculated and were given in the table 4.45 to 4.46. The $T_{50}$, $T_{90}$, DE$_{20}^{\%}$ values of LT13 tablet formulations were 7.5 min, 26 min, 73.23% respectively. The $T_{50}$, $T_{90}$, DE$_{20}^{\%}$ values of LT26 tablet formulations were 6 min, 17 min, 74.16% respectively. It was observed that as the proportion of super disintegrant is increased in the tablet, the dissolution rate and drug release from the tablets were found to be rapid. Thus lovastatin fast dissolving tablets prepared with CCS at 5 % w/w concentration (LT13 and LT26) were found to exhibit high dissolution rate compared to other tablet formulations. This was due to the increased wettability, rapid dispersion and faster drug release. Among the various super disintegrants employed for preparation of fast dissolving tablets crospovidone was found to release the drug at a faster rate when compared to others. The order of release of drug from fast dissolving tablets with various super disintegrants were CCS > CP > SSG > PGS. 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 than compared to the others and hence these two tablets were further selected for in vivo and accelerated stability studies as per ICH guidelines.

5.8. Dissolution Studies of Fast Dissolving Tablets of Simvastatin:

Dissolution studies were performed on the prepared fast dissolving tablets of simvastatin by using 8 station USP Type II dissolution apparatus with 900 ml of pH 7.0 phosphate buffer maintaining at 37±0.5°C with a paddle speed at 50rpm. These studies were performed in triplicate for all the tablets. The dissolution rate of drug from tablets prepared with various super disintegrants was compared with the tablet prepared without the super disintegrant. These studies indicated that all the tablet formulations prepared by using various super disintegrants were found to exhibit high dissolution rate than compared to the tablet prepared without super disintegrant. It was found that the tablets prepared by using the lyophilised dispersions were found to release the drug at a faster rate when compared to the tablets prepared by using dispersions of solvent evaporation. The dissolution profiles of lovastatin fast dissolving tablets were given in tables 4.37 to 4.44 and shown in the figures 4.51 to 4.58.

The first order plots were plotted by taking log% undissolved versus time (min). The slope obtained from the linear line was multiplied with 2.303 to get first order rate constant (K) for various formulations. It was observed that all the simvastatin fast dissolving tablets were found to follow the first order kinetics. The R² values obtained for all the tablets were linear and obtained in the range of 0.9573 to 0.9932. The in vitro dissolution parameters such as T₅₀, T₉₀, DE₂₀% of all the simvastatin fast dissolving tablets were calculated and were given in the table 4.47 to 4.48. The T₅₀, T₉₀, DE₂₀% values of ST13 tablet formulations were 6.5 min, 24min, 74.56% respectively. The T₅₀, T₉₀, DE₂₀% values of ST26 tablet formulations
were 6 min, 16 min, 75.66% respectively. It was observed that as the proportion of super disintegrant is increased in the tablet, the dissolution rate and drug release from the tablets were found to be rapid. Thus simvastatin fast dissolving tablets prepared with CCS at 5 % w/w concentration (ST13 and ST26) were found to exhibit high dissolution rate than compared to other tablet formulations. This was due to the increased wettability, rapid dispersion and faster drug release. Among the various super disintegrants employed for preparation of fast dissolving tablets crospovidone was found to release the drug at a faster rate when compared to others. The order of release of drug from fast dissolving tablets with various super disintegrants were CCS > CP > SSG > PGS. Based on the in vitro dissolution studies of fast dissolving tablets ST13 and ST26 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.

5.9. Comparative Dissolution Studies of Lovastatin and Simvastatin Fast Dissolving Tablets with their Marketed Formulations:

A comparative dissolution studies were performed for the formulations LT13 and LT26 containing lovastatin with the marketed tablets of lovastatin (Lostatin). The results obtained from dissolution profiles indicated that T_{50}, T_{90}, obtained for the marketed tablet were 14 min, >30 min where as for LT13 and LT26 showed T_{50}, T_{90} at 7.5 min, 26 min, and 6 min, 17 min respectively. The DE_{20} values obtained for the marketed tablet of lovastatin is 69.98% while for the fast dissolving tablets LT13 and LT26 were 73.23% and 74.16%. Thus the dissolution studies indicated that the 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 found to comply with the IP acceptance limits of dissolution testing.
A comparative dissolution studies were performed for the formulations ST13 and ST26 containing simvastatin with the marketed tablets of simvastatin (Vastatin). The results obtained from dissolution profiles indicated that $T_{50}$, $T_{90}$, obtained for the marketed tablet were 13 min, >30 min where as for ST 13 and ST 26 showed $T_{50}$, $T_{90}$ at 6.5 min, 24 min, and 6 min, 16 min respectively. The DE$_{20}$% values obtained for the marketed tablet of Simvastatin is 70.12% while for the fast dissolving tablets ST13 and ST26 were 74.56% and 75.66%. Thus the dissolution studies indicated that the fast dissolving tablets ST13 and ST26 gave improved dissolution characteristics of simvastatin than that of the marketed tablet. All the tablet formulations including marketed tablet found to comply with the IP acceptance limits of dissolution testing. Comparative dissolution profiles of LT13, LT26 with marketed tablet lostatin and ST13, ST26 with marketed tablet vastatin were sown in figures 4.67& 4.68.

5.10. In Vivo Pharmacokinetic Studies of Lovastatin Fast Dissolving Tablets

In the present study lovastatin oral solution, lovastatin fast dissolving tablets LT13 and LT26 were subjected to pharmacokinetic studies in rabbits. These formulations were administered to rabbits through oral route at dose of 10 mg/rabbit and plasma concentrations of lovastatin were determined by HPLC method as described earlier. Pharmacokinetic parameters such as concentration maximum ($C_{\text{max}}$), time of peak plasma concentration ($T_{\text{max}}$), biological half life ($t_{\frac{1}{2}}$), AUC$_{(0-t)}$, AUMC$_{(0-t)}$ and mean residence time (MRT) were calculated by using PK summit solutions software USA. Plasma drug concentrations obtained versus time plots were shown in figure 4.69 and the parameters were given in table 4.49. The orally administered lovastatin (oral solution) reached maximum concentration ($C_{\text{max}}$) of 28.71 ng/ml, time of peak plasma concentration ($t_{\text{max}}$) achieved at 1 hr with an half life of 3.89 hrs. The fast dissolving tablets LT13 and LT26 administered as oral solution achieved maximum concentration ($C_{\text{max}}$) of 38 ng/ml, 42.3 ng/ml with time of peak plasma concentration ($t_{\text{max}}$) at
0.5 hrs for both the formulations respectively. The AUC(0-t) values obtained for drug solution, LT13 and LT26 tablet formulations were 123 ng-hr/ml, 183 ng-hr/ml and 165 ng-hr/ml respectively. The mean residence time for the pure drug solution was 5.5 hrs while the tablet formulations LT13 and LT26 were upto 6.9 hrs and 6.6 hrs respectively. These results thus indicated that fast dissolving tablets LT13 and LT26 exhibited improved lovastatin plasma concentrations by extending the mean residence time with increased AUC values resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

In the present study simvastatin oral solution, simvastatin fast dissolving tablets ST13 and ST26 were subjected to pharmacokinetic studies in rabbits. These formulations were administered to rabbits through oral route at dose of 10 mg/rabbit and plasma concentrations of simvastatin were determined by HPLC method as described earlier. Pharmacokinetic parameters such as concentration maximum (C\text{max}), time of peak plasma concentration (T\text{max}), biological half life (t\text{1/2}), AUC(0-t), AUMC(0-t) and mean residence time (MRT) were calculated by using PK summit solutions software USA. Plasma drug concentrations obtained versus time plots were shown in fig 4.70. The parameters were given in table 4.50. The orally administered Simvastatin (oral solution) reached maximum concentration (C\text{max}) of 27.2 ng/ml, time of peak plasma concentration (t\text{max}) achieved at 1 hr with an half life of 3.03 hrs. The fast dissolving tablets ST 13 and ST 26 administered as oral solution achieved maximum concentration (C\text{max}) of 41.8 ng/ml, 45.6 ng/ml with time of peak plasma concentration (t\text{max}) at 0.5 hrs for both the formulations respectively. The AUC(0-t) values obtained for drug solution, ST13 and ST26 tablet formulations were 71 ng-hr/ml, 107 ng-hr/ml and 110 ng-hr/ml respectively. The mean residence time for the pure drug solution was 2.7 hrs while the tablet formulations ST13 and ST26 were upto 2.9 hrs and 2.7 hrs respectively. These results thus indicated that fast dissolving tablets ST13 and ST26 exhibited improved simvastatin
plasma concentrations by extending the mean residence time with increased AUC values resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

5.11. Accelerated Stability Studies

The fast dissolving tablets optimized for in vivo studies were subjected to accelerated stability studies as per ICH guide lines. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and drug release from the fast dissolving tablets. The tablets LT13, LT26 containing lovastatin and ST13, ST26 containing simvastatin were subjected to accelerated stability studies. The results of these studies were given in tables 4.51-4.56 and shown in figures 4.71-4.74. The results thus indicated that there were no visible and 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.