**Chapter - 6**

**Chapter - 6. DISCUSSION OF RESULTS**

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6. 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 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.

The present research work has been carried out with an aim to increase the solubility and dissolution rate of Atorvastatin Calcium and Rosuvastatin Calcium, 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.

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 1-2 hours. 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 dispersions formulations for improving its solubility and bioavailability by improving the dissolution rate.
6.1 ANALYTICAL METHODS FOR THE ESTIMATION OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM

Atorvastatin Calcium and Rosuvastatin Calcium were analysed by simple, sensitive UV spectrophotometric methods. Atorvastatin Calcium and Rosuvastatin Calcium were dissolved in methanol and then from the methanolic stock solutions standard dilutions were made with pH 6.8 phosphate buffer. Atorvastatin Calcium was estimated at wavelength 246 nm by using pH 6.8 phosphate buffer as blank. Rosuvastatin calcium was estimated at wavelength 248 nm by using pH 6.8 phosphate buffer as blank. This methods were adopted for estimation of drugs in the solid dispersions and also in in vitro dissolution studies. Atorvastatin Calcium was estimated in the concentration range of 2-10 µg/ml. Rosuvastatin Calcium 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 Atorvastatin Calcium and Rosuvastatin Calcium in pure form and in formulations. The calibration curves for the estimation of Atorvastatin Calcium and Rosuvastatin Calcium were given in tables 5.1 and 5.2 and shown in figures 5.1 and 5.2.

In vivo pharmacokinetic studies of Atorvastatin Calcium and Rosuvastatin Calcium were carried in rabbits. The Atorvastatin Calcium and Rosuvastatin Calcium concentration in the rabbit plasma was estimated by HPLC method. These methods were found to
be suitable for determining the plasma concentration of drugs. The calibration curves for the estimation of Atorvastatin Calcium and Rosuvastatin Calcium in the rabbit plasma were given in tables 5.3 and 5.4 and shown in figures 5.3 and 5.4.

6.2 SATURATED SOLUBILITY STUDIES OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM

Saturated solubility studies were performed on Atorvastatin Calcium and Rosuvastatin Calcium by using different dissolution media. These studies were performed in an orbital shaker at 37°C with 50rpm for 24 hrs. The solubility of Atorvastatin Calcium and Rosuvastatin Calcium in different dissolution media were given in tables 5.5 and 5.6. Both the drugs 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. It was also observed that pH 6.8 phosphate buffer is the official dissolution medium specified in USP for both the drugs.

6.3 PREPARATION OF SOLID DISPERSIONS OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM

Solid dispersions of Atorvastatin Calcium and Rosuvastatin Calcium were prepared by physical mixing, fusion, 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 5.7 and 5.8. 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.

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 16.96° to 24.65° which indicated good flow properties of dispersions. The Carr’s index values obtained for various solid dispersions were in the range of 12.97 to 15.96% which indicated excellent flow properties of dispersions. The pure drug form of Atorvastatin Calcium and Rosuvastatin Calcium showed angle of repose values 27.28° and 26.18° and Carr’s index values 18.61 and 18.53% respectively indicating the poor flow characteristics when compared to solid dispersions. The average particle size for all the solid dispersions were in the range of 171-179 µm. The drug content for all the dispersions were in the range of 19.41 to 20.05 mg. Thus all the solid dispersions were found to stable and suitable for compression as tablets. The physical parameters of Atorvastatin Calcium and Rosuvastatin Calcium solid dispersions were given in tables 5.9 and 5.10.
6.4 DISSOLUTION STUDIES OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM SOLID DISPERSIONS

Dissolution studies were performed on the prepared solid dispersions of Atorvastatin Calcium and Rosuvastatin Calcium by using eight station USP Type II dissolution apparatus with 900 ml of pH 6.8 phosphate buffer maintaining at 37±0.5°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 Atorvastatin Calcium and Rosuvastatin Calcium 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.

Atorvastatin Calcium solid dispersions prepared by physical mixing method were found to release the drug from 43.28% to 62.67%. It was observed that the dissolution rate of Atorvastatin Calcium was increased by 1.12 to 1.62 folds. Atorvastatin Calcium solid dispersions prepared by fusion method were found to release the drug from 70.21% to 98.89%. It was observed that the dissolution rate of Atorvastatin Calcium was increased by 1.82 to 2.57 folds. Atorvastatin Calcium solid dispersions prepared by solvent evaporation method were found to release the drug from 70.41% to 93.64%. It was observed that the dissolution rate of Atorvastatin Calcium was increased by 1.83 to 2.43 folds. Atorvastatin Calcium solid dispersions prepared by lyophilisation method were found to
release the drug from 72.45% to 99.89%. It was observed that the dissolution rate of Atorvastatin Calcium was increased by 1.88 to 2.59 folds than compared to the pure drug Atorvastatin Calcium dissolution. The pure drug Atorvastatin Calcium exhibited the dissolution rate up to only 38.45% in the pH 6.8 phosphate buffer. The dissolution profiles of pure drug Atorvastatin Calcium and the prepared solid dispersions were given in the tables 5.11 to 5.14 and shown in the figures 5.5 to 5.8.

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 Atorvastatin Calcium solid dispersions were found to follow first order kinetics. The $R^2$ values obtained for all the solid dispersions were linear and obtained in the range of 0.9735 to 0.9933. The first order plots of pure drug Atorvastatin Calcium and the prepared solid dispersions were shown in the figures 5.9 to 5.12. The in vitro dissolution parameters such as $T_{50}$, $T_{90}$, DE$_{20}$% of all the Atorvastatin Calcium solid dispersions were calculated and given in table 5.19. The $T_{50}$, $T_{90}$, DE$_{20}$% values of AF 8 dispersions were 6 min, 27.5 min, 73.57% respectively. The $T_{50}$, $T_{90}$, DE$_{20}$% values of AL 16 dispersions were 5 min, 23.5 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. Atorvastatin
Calcium solid dispersions AF 8 and AL 16 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 lyophilisation 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 lyophilisation > fusion > solvent evaporation > physical mixing. 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.

Rosuvastatin Calcium solid dispersions prepared by physical mixing method were found to release the drug from 69.71% to 84.18%. It was observed that the dissolution rate of Rosuvastatin Calcium was increased by 1.57 - 1.90 folds. Rosuvastatin Calcium solid dispersions prepared by fusion method were found to release the drug from 78.32% to 98.98%. It was observed that the dissolution rate of Rosuvastatin Calcium was increased by 1.77 - 2.23 folds. Rosuvastatin Calcium solid dispersions prepared by solvent evaporation method were found to release the drug from 73.32% to 92.54%. It was observed that the dissolution rate of Rosuvastatin
Calcium was increased by 1.65 - 2.09 folds. Rosuvastatin Calcium solid dispersions prepared by lyophilisation method were found to release the drug from 82.47% to 99.58%. It was observed that the dissolution rate of Rosuvastatin Calcium was increased by 1.86 - 2.25 folds than compared to the pure drug Rosuvastatin Calcium dissolution. The pure drug Rosuvastatin Calcium exhibited the dissolution rate up to 44.20% in pH 6.8 phosphate buffer. The dissolution profiles of pure drug Rosuvastatin Calcium and the prepared solid dispersions were given in the tables 5.15 to 5.18 and shown in the figures 5.13 to 5.16.

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 Rosuvastatin Calcium 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 first order plots of pure drug Rosuvastatin Calcium and the prepared solid dispersions were shown in the figures 5.17 to 5.20. The in vitro dissolution parameters such as $T_{50}$, $T_{90}$, DE$_{20}\%$ of all the Rosuvastatin Calcium solid dispersions were calculated and given in the table 5.20. The $T_{50}$, $T_{90}$, DE$_{20}\%$ values of RF 8 dispersions were 7.6 min, 24.3 min, 71.37\% respectively. The $T_{50}$, $T_{90}$, DE$_{20}\%$ values of RL16 dispersions were 5.8 min, 20.0 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. Rosuvastatin
Calcium solid dispersions RF 8 and RL 16 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 lyophilisation 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 lyophilisation > fusion
> solvent evaporation > physical mixing. Based on the \textit{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.

\section*{6.5 CHARACTERIZATION STUDIES OF ATORVASTATIN CALCIUM
AND ROSUVASTATIN CALCIUM SOLID DISPERSIONS}

The complex formation, crystalline characteristics of the drug
and surface characteristics of the drug were further characterised by
DSC, PXRD, IR and SEM analysis. The DSC studies were carried out
on DSC (DSC60, Schimadzu). The DSC thermogram of Atorvastatin
Calcium exhibits a sharp peak at 232.7°C. The melting endotherm of
polyethylene glycol-6000 is in the temperature range of 66.4 °C. In the
DSC thermogram of 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. The DSC thermograms of pure Atorvastatin Calcium, polyethylene glycol-6000 and Atorvastatin Calcium solid dispersions were shown in figures 5.21 to 5.24. The DSC thermogram of Atorvastatin Calcium solid dispersion indicated the formation of drug-carrier complex.

The PXRD patterns of Atorvastatin Calcium, polyethylene glycol and Atorvastatin Calcium solid dispersion (AF 8 and AL 16) were traced employing X-ray diffractometer (Bruker AXS). The diffraction pattern of pure drug Atorvastatin Calcium 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 Atorvastatin Calcium solid dispersions shows a significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks. Thus the PXRD of Atorvastatin Calcium solid dispersions (AF 8 and AL 16) indicated the amorphous form of Atorvastatin Calcium complexed in the carrier polyethylene glycol-6000. The PXRD patterns
FTIR analysis was used to know the possible interaction of drug with the carrier. Figures 5.26 to 5.29 shows the IR spectra of Atorvastatin Calcium, PEG-6000 and their optimized solid dispersions. Pure Atorvastatin Calcium a characteristic peak of N-H bending at 1651.15 cm⁻¹ and a band with main strong peak at 1965.05 cm⁻¹ indicative of the C=O stretch of the amide group. The spectrum of PEG-6000 showed important bands at 1966.5 cm⁻¹. The FTIR spectra of both the solid dispersions prepared by fusion and lyophilisation methods showed peak of esteric C=O stretch vibration of the Atorvastatin Calcium. Also a N-H vibration peak was still detected at the same position as that of Atorvastatin Calcium. Consequently, the FTIR spectra of the optimized solid dispersions seemed to be only a summation of Atorvastatin Calcium and PEG-6000. This result suggested that there was no interaction between Atorvastatin Calcium and PEG-6000 in their combinations.

SEM photomicrographs that reveal the surface morphology of sample were taken by a scanning electron microscope (JSEM 6390). In the SEM photomicrographs of pure Atorvastatin Calcium characteristic needle shaped crystals were observed. SEM photomicrographs of Atorvastatin Calcium solid dispersions prepared by fusion 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 Atorvastatin Calcium, and Atorvastatin Calcium solid dispersions (AF 8, AL 16) were shown in figures 5.30 to 5.32.

The DSC studies were carried out on DSC calorimeter (DSC60, Schimadzu). The DSC thermogram of Rosuvastatin Calcium exhibits a sharp peak at 231.2°C. The melting endotherm of polyethylene glycol-6000 is in the temperature range of 66.4°C. In the DSC thermogram of 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. The DSC thermograms of pure Rosuvastatin Calcium, polyethylene glycol-6000 and Rosuvastatin Calcium solid dispersions were shown in figures 5.33 to 5.36. The DSC thermogram of Rosuvastatin Calcium solid dispersion indicated the formation of drug-carrier complex.

The PXRD patterns of Rosuvastatin Calcium, polyethylene glycol and Rosuvastatin Calcium solid dispersion (RF 8 and RL 16) were traced employing X-ray diffractometer (Bruker AXS). The diffraction pattern of pure drug Rosuvastatin Calcium 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 Rosuvastatin Calcium solid dispersions shows a significant decrease in the crystallinity as evident by the disappearance of sharp distinctive peaks. Thus the PXRD of Rosuvastatin Calcium solid dispersions (RF 8 and RL 16) indicated the amorphous form of Rosuvastatin Calcium complexed in the carrier polyethylene glycol-6000. The PXRD patterns of pure Rosuvastatin Calcium, polyethylene glycol-6000 and Rosuvastatin Calcium solid dispersions were shown in figure 5.37.

FTIR analysis was used to know the possible interaction of drug with the carrier. Figures 5.38 to 5.41 shows the IR spectra of Rosuvastatin Calcium, PEG-6000 and their optimized solid dispersions. Pure Rosuvastatin Calcium a characteristic peak of S=O stretching at 1154.89 cm$^{-1}$ and a band with main strong peak at 3378.06 cm$^{-1}$ indicative of the O-H stretch of the carboxylic group. The spectrum of PEG-6000 showed important bands at 1966.65 cm$^{-1}$. The FTIR spectra of both the solid dispersions prepared by fusion and lyophilisation methods showed peak of carboxylic O-H stretch vibration of the Rosuvastatin Calcium. Also a S=O vibration peak was still detected at the same position as that of Rosuvastatin Calcium. Consequently, the FTIR spectra of the optimized solid dispersions seemed to be only a summation of Rosuvastatin Calcium and PEG-
6000. This result suggested that there was no interaction between Rosuvastatin Calcium and PEG-6000 in their combinations.

SEM photomicrographs that reveal the surface morphology of sample were taken by a scanning electron microscope (JSEM 6390). In the SEM photomicrographs of pure Rosuvastatin Calcium characteristic needle shaped crystals were observed. SEM photomicrographs of Rosuvastatin Calcium solid dispersions prepared by fusion 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 Rosuvastatin Calcium, and Rosuvastatin Calcium solid dispersions (RF 8, RL 16) were shown in figures 5.42 to 5.44.

6.6 PREPARATION OF FAST DISSOLVING TABLETS OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM

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. 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 Elite 10 station mini press. All the batches of tablets were compressed under similar conditions to avoid processing variables. The composition of various tablet formulations of
Atorvastatin Calcium And Rosuvastatin Calcium were give in tables 5.21 to 5.24. 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/cm². The uniformity of weight of different batches of tablets was in the range of 197-204 mg. The friability of different batches of tablets was in the range of 0.15-0.32%. 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 57-182 sec. Drug content in the different batches of tablets were in the range of 19.56-20.10 mg. The physical parameters of various Atorvastatin Calcium and Rosuvastatin Calcium fast dissolving tablets were given in the tables 5.25 to 5.28.

6.7 DISSOLUTION STUDIES OF FAST DISSOLVING TABLETS OF ATORVASTATIN CALCIUM

Dissolution studies were performed on the prepared fast dissolving tablets of Atorvastatin Calcium by using 8 station USP Type II dissolution apparatus with 900 ml of pH 6.8 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 fusion.
The dissolution profiles of Atorvastatin Calcium fast dissolving tablets
were given in the tables 5.29 to 5.36 and shown in the figures 5.45 to
5.52.

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 Atorvastatin Calcium 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 0.9833 to 0.9993. The first order plots of Atorvastatin
Calcium fast dissolving tablets were shown in the figures 5.53 to 5.60.
The in vitro dissolution parameters such as T_{50}, T_{90}, DE_{20}\% for all the
Atorvastatin Calcium fast dissolving tablets were calculated and were
given in the tables 5.45 to 5.46. The T_{50}, T_{90}, DE_{20}\% values of AT13
tablet formulations were 8.2 min, 25.5 min, 73.23\% respectively. The
T_{50}, T_{90}, DE_{20}\% values of AT 26\textsuperscript{6} tablet formulations were 5.4 min,
15.4 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
Atorvastatin Calcium fast dissolving tablets prepared with CCS at 5 %
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w/w concentration (AT 13 and AT 26) 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 croscarmellose sodium 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 AT 13 and AT 26 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.

6.8 DISSOLUTION STUDIES OF FAST DISSOLVING TABLETS OF
ROSUVASTATIN CALCIUM

Dissolution studies were performed on the prepared fast
dissolving tablets of Atorvastatin Calcium by using 8 station USP Type
II dissolution apparatus with 900 ml of pH 6.8 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 fusion.
The dissolution profiles of Rosuvastatin Calcium fast dissolving
tablets were given in the tables 5.37 to 5.44 and shown in the figures
5.61 to 5.68.

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 Rosuvastatin Calcium 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 0.9856 to 0.9980. The first order plots of Rosuvastatin
Calcium fast dissolving tablets were shown in the figures 5.69 to 5.76.
The *in vitro* dissolution parameters such as $T_{50}$, $T_{90}$, DE$_{20}$% for all the
Rosuvastatin Calcium fast dissolving tablets were calculated and were
given in the tables 5.47 to 5.48. The $T_{50}$, $T_{90}$, DE$_{20}$% values of RT 13
tablet formulations were 7.7 min, 27.1 min, 73.23% respectively. The
$T_{50}$, $T_{90}$, DE$_{20}$% values of RT 26 tablet formulations were 5.0 min,
15.0 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
Rosuvastatin Calcium fast dissolving tablets prepared with CCS at 5
% w/w concentration (RT 13 and RT 26) 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 croscarmellose sodium 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 RT 13 and RT 26 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.

A comparative dissolution studies were performed for the formulations AT 13, AT 26 containing Atorvastatin Calcium and RT 13, RT 26 containing Rosuvastatin Calcium with the marketed tablets of Atorvastatin Calcium and Rosuvastatin Calcium. The results obtained from dissolution profiles indicated that $T_{50}$, $T_{90}$, obtained for the marketed tablet of Atorvastatin Calcium were 14.0 min, >30 min where as for Atorvastatin Calcium fast dissolving tablet AT 13 and AT 26 showed 8.2 min, 25.2 min and 5.4 min, 15.4 min respectively. The DE$_{20}$% values obtained for the marketed tablet of Atorvastatin Calcium is 70.12% while for the fast dissolving tablets AT 13 and AT 26 were 74.56% and 75.66%. Thus the dissolution studies indicated that the fast dissolving tablets AT 13 and AT 26 gave improved
dissolution characteristics of Atorvastatin Calcium than that of the marketed tablet.

The results obtained from dissolution profiles indicated that $T_{50}$, $T_{90}$, obtained for the marketed tablet of Rosuvastatin Calcium were 13.0 min, >30 min whereas for Rosuvastatin Calcium fast dissolving tablet RT 13 and RT 26 showed 5.0 min, 15.0 min and 7.7 min, 27.1 min respectively. The DE$_{20}$% values obtained for the marketed tablet of Rosuvastatin Calcium is 70.12% while for the fast dissolving tablets RT 13 and RT 26 were 74.56% and 75.66%. Thus 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 found to comply with the IP acceptance limits of dissolution testing. Comparative dissolution profiles of AT 13, AT 26 with marketed tablet and RT 13, RT 26 with marketed tablet were given in tables 5.49 to 5.50 shown in figures 5.77 to 5.78.

6.9 IN VIVO PHARMACOKINETIC STUDIES OF ATORVASTATIN CALCIUM FAST DISSOLVING TABLETS

In the present study Atorvastatin Calcium oral suspension, Atorvastatin Calcium fast dissolving tablets AT 13 and AT 26 were subjected to pharmacokinetic studies in rabbits. These formulations were administered to rabbits through oral route at dose of 10 mg/kg body weight and plasma concentrations of Atorvastatin Calcium 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 ($t_{\frac{1}{2}}$), $\text{AUC}_{[0-t]}$, $\text{AUMC}_{[0-t]}$ 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 5.79 and the parameters were given in table 5.51. The orally administered Atorvastatin Calcium (oral suspension) reached maximum concentration ($C_{\text{max}}$) of 598.0 ng/ml, time of peak plasma concentration ($t_{\text{max}}$) achieved at 120 min with an half life of 776.2 min. The fast dissolving tablets AT 13 and AT 26 administered as oral solution achieved maximum concentration ($C_{\text{max}}$) of 864.4 ng/ml, 873.7 ng/ml with time of peak plasma concentration ($t_{\text{max}}$) at 110 min, 105 min for both the formulations respectively. The $\text{AUC}_{[0-t]}$ values obtained for drug solution, AT 13 and AT 26 tablet formulations were 184342 ng-min/ml, 283039 ng-hr/ml and 293894 ng-hr/ml respectively. The mean residence time for the pure drug solution was 675.2 min while the tablet formulations AT 13 and AT 26 were upto 733.2 min and 762.6 min respectively. These results thus indicated that fast dissolving tablets AT 13 and AT 26 exhibited improved Atorvastatin Calcium plasma concentrations by extending the mean residence time with increased AUC values resulted in improved dissolution rate, faster onset of action with enhanced bioavailability.

6.10 IN VIVO PHARMACOKINETIC STUDIES OF ROSUVASTATIN CALCIUM FAST DISSOLVING TABLETS

In the present study Rosuvastatin Calcium oral solution, Rosuvastatin Calcium fast dissolving tablets RT 13 and RT 26 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 Rosuvastatin Calcium 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 ($t_{1/2}$), 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 5.80. The parameters were given in table 5.52. The orally administered Rosuvastatin Calcium (oral solution) reached maximum concentration ($C_{\text{max}}$) of 478.2 ng/ml, time of peak plasma concentration ($t_{\text{max}}$) achieved at 300 min with an half life of 526.5 min. The fast dissolving tablets RT 13 and RT 26 administered as oral solution achieved maximum concentration ($C_{\text{max}}$) of 786.2 ng/ml, 803.6 ng/ml with time of peak plasma concentration ($t_{\text{max}}$) at 200 min for both the formulations respectively. The AUC$_{(0-t)}$ values obtained for drug solution, RT 13 and RT 26 tablet formulations were 220140 ng-min/ml, 422460 ng-hr/ml and 435821 ng-hr/ml respectively. The mean residence time for the pure drug solution was 747.3 min while the tablet formulations RT 13 and RT 26 were upto 766.0 min and 847.3 min respectively. These results thus indicated that fast dissolving tablets RT 13 and RT 26 exhibited improved Rosuvastatin Calcium plasma concentrations by extending the mean residence time with increased AUC values resulted in
improved dissolution rate, faster onset of action with enhanced bioavailability.

6.11 ACCELERATED STABILITY STUDIES OF ATORVASTATIN CALCIUM AND ROSUVASTATIN CALCIUM FAST DISSOLVING TABLETS

The fast dissolving tablets optimized for \textit{in vivo} studies were subjected to accelerated stability studies as per ICH guidelines. 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 AT 13, AT 26 containing Atorvastatin Calcium and RT 13, RT 26 containing Rosuvastatin Calcium were subjected to accelerated stability studies. The results of these studies were given in tables 5.53 to 5.58 and shown in figures 5.81 to 5.84. 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 AT 13, AT 26 of Atorvastatin Calcium and RT 13, RT 26 of Rosuvastatin Calcium were found to be quite stable.