3. MATERIALS

1. Lovastatin
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

2. Simvastatin
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

3. Gemfibrozil
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

4. Polytethylene glycol-6000
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

5. Croscarmellose sodium
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

6. Crospovidone
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

7. Pregelatinized starch
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

8. Sodium starch glycolate
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

9. Potassium dihydrogen Phosphate
   (S.D Fine Chem Ltd., Mumbai)

10. Sodium hydroxide
    (S.D Fine Chem Ltd., Mumbai)

11. Talc
    (S.D Fine Chem Ltd., Mumbai)

12. Magnesium Stearate
    (S.D Fine Chem Ltd., Mumbai)
13. Hydrochloric acid
   (S.D Fine Chem Ltd., Mumbai)

14. Methanol
   (S.D Fine Chem Ltd., Mumbai)

15. Aspartame
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

16. Ammonium Acetate
   (S.D Fine Chem Ltd., Mumbai)

17. Acetonitrile
   (S.D Fine Chem Ltd., Mumbai)
3.2. ANALYTICAL METHODS

3.2.1 Estimation of Lovastatin

A spectrophotometric method based on the measurement of absorbance at 238nm in 7.0 pH phosphate buffer was used in the present study for estimation of lovastatin. (Mehardad, 2009)

**Standard Solution:**

100 mg of lovastatin was weighed and dissolved in methanol in a 100 ml volumetric flask and the solution was made up to volume with methanol.

**Procedure:**

Standard solution of lovastatin was subsequently diluted with 7.0 pH phosphate buffer to obtain series of dilutions containing 2,4,6,8,10 µg of Lovastatin per 1ml of solution. The absorbance of the above solutions were measured in Elico double beam UV spectrophotometer at 238nm using 7.0 pH phosphate buffer as blank. Concentration of lovastatin and corresponding absorbance values were given in table 4.1. The absorbance values were plotted against concentration of Lovastatin as shown in fig 4.1. The method obeys the beer's law in the concentration range of 0-10 µg /ml. Reproducibility of the method was tested by analyzing six separately weighed samples of lovastatin. Thus the method was found to be suitable for the estimation of lovastatin in dissolution fluids. Calibration curve shown in figure 4.1 was used for the estimation of Lovastatin.
3.2.2. Estimation of Simvastatin

A spectrophotometric method based on the measurement of absorbance at 239nm in 7.0 pH phosphate buffer was used in the present study for the estimation of simvastatin. (Balaji, 2010).

Standard Solution:

100 mg of simvastatin was weighed and dissolved in methanol in a 100 ml volumetric flask and the solution was made up to volume with methanol.

Procedure

Standard solution of simvastatin was subsequently diluted with 7.0 pH phosphate buffer to obtain series of dilutions containing 2, 4, 6, 8, 10 µg of Simvastatin per 1ml of solution. Absorbances of the above solutions were measured in Elico double beam UV spectrophotometer at 239nm using 7.0 pH phosphate buffer as blank. The concentration of simvastatin and corresponding absorbance values are given in table 4.2. The absorbance values were plotted against concentration of simvastatin as shown in fig 4.2. The method obeys the beer's law in the concentration range of 0-10 µg /ml. Reproducibility of the method was tested by analyzing six separately weighed samples of simvastatin. Thus the method was found to be suitable for the estimation of simvastatin in dissolution fluids. Calibration curve shown in figure 4.2 was used for the estimation of simvastatin.

3.2.3. Assay of Lovastatin in Rabbit Plasma:

The plasma concentration of lovastatin was estimated by HPLC method. (Islam Ullah, 2010). A working standard lovastatin (12mg/ml) and internal standard solution gemfibrozil (12 mg/ml) in pH 5.0 buffer was prepared. The standard drug solutions containing 0.4, 0.8, 1.6, 5, 10, 20, 50 ng/ml were made in plasma by adding appropriate volumes of the standard
solution in centrifuge tubes, each containing 1ml of plasma, 1ml of internal standard solution was then added in each tube, vortexed manually for 30 seconds, then 3ml acetonitrile was added in each tube and again vortexed for 3 minutes. The solution was centrifuged for 10 minutes at 3500 rpm to precipitate the plasma protein. One half of the supernatant out of the total volume of the solution was taken in a glass vial and evaporated it at 40°C in incubator. To each vial, 2ml of mobile phase was added, dissolved by gentle shaking, filtered and analyzed immediately. A volume of 20 μl of reconstituted solution was injected in to the HPLC system. (Agilent 10 AS pump, 10A UV-Vis detector, SCL-10A system controller and class CR 10 soft were as data processor on-line with reverse phase C18 column (inert-sil ODS-2, 4.6×250 nm, 5 μm particle size and pre column). Mobile phase consisted of 0.1 M ammonium acetate buffer (pH 5.0) and acteonitrile in the ratio of 28:72 (v/v), the flow rate was 1.5 ml/min. Analysis was monitored at 238 nm. The plot of peak ratio of lovastatin to gemfibrozil against the concentration of lovastatin in plasma was linear up to 50 ng/ml. The limit of quantification of lovastatin with this method is 0.4 ng/ml and the mean percent drug recovered for the above concentration range was 86.5% indicating the method is reproducible. It was given in table 4.3 and shown in figure 4.3.

3.2.4 Assay of Simvastatin in Rabbit Plasma:

The plasma concentration of simvastatin was estimated by HPLC method. (Yang, 2003). Stock solution of simvastatin and lovastatin were prepared in methanol (1 mg/ml) and were further individually diluted with methanol to obtained the desired concentrations. The stock solutions were kept refrigerated and restored to room temperature before use. The stock solution was appropriately diluted with methanol to obtain internal standard (100 ng/ml) solution and solutions for calibration at 5, 10, 25, 50, 100, 250, 500 and 1000 ng/ml of simvastatin. A 0.5ml volume of drug free plasma was placed in a 5ml centrifuge tube, then 10 μl of serial simvastatin stock solution and 10 μl of internal standard were added. To 0.5 ml
volume of plasma placed in a centrifuge tube 10 µl of internal standard was added. After a thorough vortex mixing for 30 seconds, mixtures were extracted with 2 ml of methyl tert-butyl ether, vortex-mixed for 3 min, and centrifuged at 4000 rpm for 10 min. 1.5ml of organic layer was removed to another centrifuge tube and evaporated under a steam of nitrogen gas in the thermostatically controlled water bath maintained at 40°C until completely dry. The dried residue obtained was dissolved in 100 µl of methanol, vortex-mixed for 2 min, centrifuged at 12000 rpm. A volume of 20 µl of reconstituted solution was injected in to the HPLC system. (Agilent 10 AS pump, 10A UV-Vis detector, SCL-10A system controller and class CR 10 soft were as data processor on-line with reverse phase C18 column (inert-sil ODS-2, 4.6×250 nm, 5 µm particle size and pre column). Mobile phase consisted of methanol: water: 5M ammonium acetate 90:10:0.1 (v/v/v). The flow rate was 0.4 ml/min. Analysis was monitored at 240 nm. The plot of peak ratio of simvastatin to lovastatin against the concentration of simvastatin in plasma was linear up to 20 ng/ml. The limit of quantification of simvastatin with this method was 0.1 ng/ml and the mean percent drug recoverd for the above concentration range was 92.5% indicating the method is reproducible. It was given in table 5.4 and shown in figure 4.4.

3.3. SATURATED SOLUBILITY STUDIES

3.3.1 Saturated Solubility Studies of Lovastatin

Saturated solubility studies of lovastatin were performed in different dissolution media. 500mg of lovastatin was weighed and transferred into different conical flasks. 50ml of different dissolution media were transferred into individual conical flasks and were closed appropriately (Srinivas, 2008). All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37°C ± 1°C for 24 hrs. Then the conical flasks were removed from the incubator shaker and the samples were filtered by using
whatman filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 238 nm by using corresponding dissolution media as blank solutions. The solubility of Lovastatin in different dissolution media were given in table 4.5.

3.3.2 Saturated Solubility Studies of Simvastatin

Saturated solubility studies of simvastatin were performed in different dissolution media. 500mg of simvastatin was weighed and transferred into different conical flasks. 50ml of different dissolution media were transferred into individual conical flasks and were closed appropriately. All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37° C ± 1° C for 24 hrs. Then the conical flasks were removed from the incubator shaker and the samples were filtered by using whatman filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 239 nm by using corresponding dissolution media as blank solutions. The solubility of Simvastatin in different dissolution media were given in table 4.6.

3.4. PREPARATION OF SOLID DISPERSIONS

Solid dispersions of lovastatin and simvastatin were prepared by using polyethylene glycol-6000 as a carrier by employing different techniques. The carrier concentration was maintained constant in the investigation. The methods employed for the preparation of solid dispersions are:

1. Physical mixing.
2. Fusion method
3. Solvent evaporation
4. Lyophilization

3.4.1. Physical Mixing:

Specified quantity of drug and polyethylene glycol 6000 were weighed separately and passed separately through sieve no 80. The materials passed through sieve no.80 were collected and transferred into a clean and dry glass mortar. Drug and PEG-6000 were triturated together and again screened through sieve no 100. The mixture passed through sieve no 100 was collected and packed in a wide mouthed amber coloured glass container and was hermetically sealed. Then the mixture was stored at ambient conditions.

3.4.2. Fusion Method:

Specified quantity of PEG-6000 was taken in a china dish and it was heated at on a mantle until molten mass was formed. To the molten mass specified quantity of drug was added and triturated vigorously at room temperature. The mixture obtained was triturated thoroughly in a glass mortar and screened through sieve no.100. Then the mixture was collected, packed in a wide mouthed amber coloured glass container and was hermetically sealed. Then the mixture was stored at ambient conditions.

3.4.3. Solvent Evaporation:

Specified quantity of drug was taken in a china dish and it was dissolved in few ml of methanol. To the methanolic solution, specified amount of PEG-6000 was added and the solvent was evaporated under vacuum using Rota flash evaporator. The mixture obtained was triturated thoroughly in a glass mortar and screened through sieve no.100. Then the mixture was collected, packed in a wide mouthed amber coloured glass container and was hermetically sealed. Then the mixture was stored at ambient conditions.
3.4.4. Lyophilization:

Specified quantity of drug and PEG-6000 were weighed added with minimum amount of water. This dispersion was rapidly solidified by freezing in the IlShin freeze drier (Shin Lab Co., Ltd). The solvent in the dispersion was sublimed under a pressure of 10M torr and condensed onto a -40°C condenser. After the solvent was completely removed, the powder residue appeared as a porous, light and puffy mass. The lyophilized preparations were stored in a dessicator at room temperature. The compositions of various solid dispersions were given in tables 4.7 & 4.8.

3.5. EVALUATION OF SOLID DISPERSIONS

Physical parameters such as Angle of Repose, Carr’s Index, Average particle size and Drug content were evaluated for prepared tablets as per the standards of official compendium.

3.5.1 Angle of Repose:

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table (Neumann, 1953). The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( h = \) Height of the pile; \( r = \) Radius of the pile.

The flow properties of different batches of solid dispersions were given in tables 4.9 & 4.10.
Specifications of Angle of Repose

<table>
<thead>
<tr>
<th>Angle of repose(degrees)</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Excellent</td>
</tr>
<tr>
<td>20-30</td>
<td>good</td>
</tr>
<tr>
<td>30-34</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

3.5.2 Carr’s Index:

It is the propensity of a powder to be compressed.

**Method**

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. (Dahlinder, 1982) Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

\[
\text{Carr’s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100
\]

**Specifications of Carr’s Index**

<table>
<thead>
<tr>
<th>Carr’s Index</th>
<th>Type of Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15</td>
<td>Excellent</td>
</tr>
<tr>
<td>12-16</td>
<td>good</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair to passable</td>
</tr>
<tr>
<td>23-35</td>
<td>poor</td>
</tr>
<tr>
<td>33-38</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Extremely poor</td>
</tr>
</tbody>
</table>
The flow properties of different formulations were shown in tables 4.9 & 4.10.

3.5.3 Particle Size Determination:

The average particle size of the prepared solid dispersions was analyzed by simple sieve analysis method (Arambulo, 1953). The average particle size of different formulations was shown in tables 4.9 & 4.10.

3.5.4. Drug Content Uniformity:

a) Lovastatin:

Solid dispersions of lovastatin from a batch were taken at random and was transferred into a 100ml volumetric flask and 70ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100ml by adding methanol. About 10ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Whatmann filter. Then the filtrate was subsequently diluted with 7.2 pH phosphate buffer and the absorbance was measured at 238nm. This test was repeated six times (n=10) for each batch of tablets. The amount of lovastatin estimated from different batches were depicted in table 4.9.

b) Simvastatin

Solid dispersions of simvastatin from a batch were taken at random and was transferred into a 100ml volumetric flask and 70ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100ml by adding methanol. About 10ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using
Whatmann filter. Then the filtrate was subsequently diluted with 7.0 pH phosphate buffer and the absorbance was measured at 239nm. This test was repeated six times (n=10) for each batch of tablets. The amount of simvastatin estimated from different batches were depicted in table 4.9.

3.6. DRUG RELEASE STUDIES FROM SOLID DISPERSIONS

3.6.1. Lovastatin Solid Dispersions:

Dissolution studies on solid dispersions were performed in a calibrated eight stage dissolution rate test apparatus equipped with paddles employing 900 ml of 7.0 pH phosphate buffer as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with equal volume to maintain the constant volume of dissolution medium throughout the experiment. Drug content of the samples was determined by Elico double beam UV spectrophotometer at 238 nm after suitable dilutions of the samples. The drug release from solid dispersions were conducted in triplicate. The dissolution profiles were depicted in tables 4.11 to 4.14 and shown in figures 4.5 to 4.8. The first order profiles were shown in figures 4.13 to 4.16. The release rate constants, T_{50}, T_{90}, DE_{20}% were given in table 4.19.

3.6.2. Simvastatin Solid Dispersions:

Dissolution studies on solid dispersions were performed in a calibrated eight stage dissolution rate test apparatus equipped with paddles employing 900 ml of 7.0 pH phosphate buffer as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with equal volume to maintain the constant volume of
dissolution medium throughout the experiment. Drug content of the samples was determined by Elico double beam UV spectrophotometer at 239 nm after suitable dilutions of the samples. The drug release from solid dispersions were conducted in triplicate. The dissolution profiles were depicted in tables 4.15 to 4.18 and shown in fig 4.9 to 4.12. The first order profiles were shown in fig 4.17 to 4.20. The release rate constants, $T_{50}$, $T_{90}$, $DE_{20}\%$ were given in table 4.20.

**3.7. CHARACTERIZATION OF SOLID DISPERSIONS**

Based on the dissolution studies performed on all the solid dispersions, some of the optimized solid dispersions were selected and further investigated for XRD, DSC and SEM studies.

**3.7.1. Differential Scanning Calorimetry (DSC):**

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of solid dispersions prepared by fusion, solvent evaporation and lyophilization methods representing the rate of heat uptake. About 10mg of sample was weighed in a standard open aluminium pans, and scanned from 20-300°C, at a heating rate of 10°C/minute while being purged with dry nitrogen. The DSC thermograms of various solid dispersions were shown figures 4.21 to 4.23 & 4.28 to 4.30.

**3.7.2 Powder X-Ray Diffractometry:**

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer Bruker AXS, DH Advance, Germany for all the samples using Ni filter, CuK ($\lambda$) radiation, a voltage of kV, a current of 20mA and receiving slit of 0.2 The samples were analyzed over 20 range of 5° to 60°, with scan step size of 0.020 °(20) and scan step time of 1 second. The DSC thermograms of various solid dispersions were shown figures 4.24 & 4.31.
3.7.3 Scanning Electron Microscopy (SEM):

The samples were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 15kV. The SEM photographs were shown in figures 4.25 to 4.27 & 4.32 to 4.34.

3.8. PREPARATION OF TABLETS WITH SOLID DISPERSIONS

Among the solid dispersions prepared and based upon the dissolution studies performed, Four (LS12, LL16, SS12, SS16) optimized dispersions were selected for further preparation as tablets. The tablets of lovastatin and simvastatin were prepared by direct compression process. The tablet formulations consisted of drug, polymer, and diluents. The ratio of drug and polymer were maintained constant while the superdisintegrant concentration was varied. The weights of all the tablet formulations were maintained uniformly by using directly compressible lactose as diluent. The compositions of various tablet formulations were given in tables 4.21 to 4.24.

The materials were individually weighed, passed through sieve no: 80 and blended for 15 minutes by using double cone blender. The powder mixture was then lubricated with 1% talc and magnesium stearate and directly compressed as tablets using Elite 10 station mini press. To minimize the processing variables all batches of tablets were compressed under identical conditions. The compressed tablets were further evaluated for their physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion time and drug content.
3.9. EVALUATION OF PHYSICAL PARAMETERS OF TABLETS

Physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for prepared tablets as per the standards of official compendium.

3.9.1. Weight Uniformity:

Twenty tablets from each batch at random were taken and weighted. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight that was already calculated. The deviation if any in the weight of individual tablets from the average weight was checked. This test highly describes that all tablets of a particular batch should be uniform in weight. If any weight variation is there, that should be within the I.P limits. The test was considered correct if not more that two tablets fall outside the I.P limits out of twenty tablets taken for the test. The weight ranges of different batches of tablets were depicted in tables 4.25 to 4.28

<table>
<thead>
<tr>
<th>Average Weight</th>
<th>Percentage Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>More than 80mg but less</td>
<td>7.5</td>
</tr>
<tr>
<td>250 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>
3.9.2. Hardness:

Hardness of the tablets were determined by using Monsanto hardness tester (Tabmachines, Mumbai). The tablet to be tested is held between fixed and moving jaw and reading of the indicator adjusted to zero. Then force to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg/cm$^2$ to break the tablet. Hardness of different batches of tablets was given in tables 4.25 to 4.28. The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression.

3.9.3. Friability:

Friability test was performed by using Roche friabilator (Remi Equipments, Mumbai). Twenty tablets of a batch were weighted and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated friability. The acceptance limits of weight loss should not be more than 1.0%. This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. These friability values were given in tables 4.25 to 4.28.

3.9.4. Wetting Time:

A piece of tissue paper folded double was placed in clean and dry petri plates containing 10 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The results obtained were given in tables 4.25 to 4.28.
3.9.5. Dispersion Time:

2 tablets were placed in 100 ml of water and stirred till completely dispersed. The dispersion time was noted for different formulations and the results obtained were given in table 4.25 to 4.28

3.9.6 Drug Content Uniformity:

a) Lovastatin:

One tablet of Lovastatin from a batch was taken at random and was crushed to a fine powder. The powdered material was transferred into a 100ml volumetric flask and 70ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100ml by adding methanol. About 10ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Whatmann filter. Then the filtrate was subsequently diluted with 7.0 pH phosphate buffer and the absorbance was measured at 238nm. This test was repeated six times (n=10) for each batch of tablets. The amount of Lovastatin estimated from different batches were depicted in tables 4.25 & 4.26.

b) Simvastatin:

One tablet of simvastatin from a batch was taken at random and was crushed to a fine powder. the powdered material was transferred into a 100ml volumetric flask and 70ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100ml by adding methanol. About 10ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Whatmann filter. Then the filtrate was subsequently diluted with 7.0pH phosphate buffer and the absorbance was measured at 239nm. This test
was repeated six times (n=6) for each batch of tablets. The amount of Simvastatin estimated from different batches were depicted in tables 4.27 & 4.28.

3.10. DRUG RELEASE STUDIES FROM TABLETS

3.10.1. Lovastatin Tablet Formulations:

Dissolution studies on each tablet formulation were performed in a calibrated eight stage dissolution rate test apparatus equipped with paddles employing 900 ml of 7.0 pH phosphate buffer as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±0.5°C through out the experiment. Samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with equal volume to maintain the constant volume of dissolution medium throughout the experiment. Drug content of the samples was determined by Elico double beam UV spectrophotometer at 238 nm after suitable dilutions of the samples. The drug release from solid dispersions were conducted in triplicate. The dissolution profiles were depicted in tables 4.29 to 4.36 and shown in figures 4.37 to 4.42. The first order release profiles were shown in figures 4.43-4.50 The release rate constants, $T_{50}$, $T_{90}$, $DE_{20\%}$ were given in tables 4.45 & 4.46

3.10.2. Simvastatin Tablet Formulations:

Dissolution studies on each tablet formulation were performed in a calibrated eight stage dissolution rate test apparatus equipped with paddles employing 900 ml of 7.0 pH phosphate buffer with 0.5% SLS as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±0.5°C through out the experiment. Samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with equal volume to maintain the constant volume of dissolution medium throughout the experiment. Drug content of the samples was determined by Elico double beam UV spectrophotometer at 239 nm after
suitable dilutions of the samples. The drug release from solid dispersions were conducted in triplicate. The dissolution profiles were depicted in tables 4.37-4.44 and shown in figures 4.51-4.58. The first order release profiles were shown in figures 4.59 to 4.66. The release rate constants, $T_{50}$, $T_{90}$, $DE_{20}\%$ were given in tables 4.47 & 4.48.

3.11. PHARMACOKINETIC STUDIES OF LOVASTATIN AND SIMVASTATIN

Male white rabbits weighing between 1.6 to 2.2 kg were used for in vivo studies of orally administered Lovastatin and Simvastatin. Animals were housed at 25 ± 1°C in air conditioned room at a relative humidity of 60 ± 5% and were provided with water and standard rabbit feed. Animals were fasted for 24 hrs prior to the administration of the drug formulation, but had free access to water. The solid dispersion mixture was administered in the solution form with a soft plastic tube (Lovastatin 10 mg/rabbit) (Simvastatin 10 mg/rabbit) to another group of animals. About 2.0 ml of blood was collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hrs, after oral solution administration from marginal ear vein into the tubes containing heparin and the plasma was separated immediately. The plasma samples were analyzed for plasma Lovastatin and Simvastatin concentration by the HPLC method as described earlier.

Pharmacokinetic Parameters:

The pharmacokinetic parameters such as maximum plasma concentration ($C_{\text{max}}$), time to reach peak plasma concentration ($t_{\text{max}}$), $AUC_{(0-t)}$, $AUMC_{(0-t)}$, $t\frac{1}{2}$ and MRT were calculated using the PK summit solutions software. The data was given in tables 4.49 to 4.50 and shown in figures 4.69 to 4.70.
3.12. ACCELERATED STABILITY STUDIES

The tablet formulations which showed good *in vivo* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and chemical stability of fast dissolving tablets containing drugs.

The tablet formulations such as LT13, LT26, & ST13, ST26 were subjected to accelerated stability studies. The above said formulations were kept in petri dishes after preparation and stored in thermostated oven at a temperature and relative humidity of 25 ± 2°C, 60 ± 5% RH for 6 months and 40 ± 2°C, 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters.

The tablets were evaluated for physical parameters and drugs were analyzed for drug content uniformity by a known spectrophotometric method as described earlier. Further these were subjected to drug release studies as stated earlier. The data was given in tables 4.51 to 4.56 and shown in figures 4.71 to 4.74.