Summary and Conclusion:  

- Simvastatin is a derivative of lovastatin and potent competitive inhibitor of HMGCO-A reductase, a rate-limiting enzyme in cholesterol biosynthesis used in the treatment of hypercholesteremia.  
- Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα).  
- However, the low solubility and poor dissolution of these molecules affects its rate of absorption, resulting in a low and variable oral bioavailability. Hence it becomes necessary to develop lipid based formulations of these molecules with enhanced solubility.  
- Solubility of drug in various oils and surfactants were carried out in order to screen the components to be used for formulation development. Drugs solubility profile was determined in various oils and surfactants, it was found that simvastatin exhibits high solubility in oleic acid (oil), cremophore RH 40(surfactant),and Transcutol p (co-surfactant). Whereas fenofibrate exhibits high solubility in meglyoil (oil), Tween 80 (surfactant), and PEG- 400 (co-surfactant).  
- The obtained spectrums of different surfactants & Oil were showed no degradation of drug formulation Pure fenofibrate spectra showed sharp characteristic peaks at 2990, 1740, 1660,and 1600cm⁻¹.  
- The nature of peak did not vary in nanoemulsion formulation indicate that there was no interaction between the drug and excipients(i.e surfactants & Oils) in the formulation. The FTIR spectrum of pure simvastatin has three characteristic peaks at 3548, 2969, and 1698cm⁻¹ for O–H stretching vibration, C-H vibration and ester stretching vibration and lactone carbonyl functional group respectively. The FTIR spectrum of pure Formulation has three characteristic peaks at 3417cm⁻¹, 2925cm⁻¹ and at 1732cm⁻¹.  
- Pseudo ternary phase diagrams were constructed by titration of a series of mixtures of oil, surfactant & cosurfactants with deionized water at room temperature by Winsor II model.
Formulations were prepared using ratios of components determined from phase diagrams. Sonicated and vortex mixing was applied to hasten the process.

Optimized formulation was subjected to freeze Thaw cycling, centrifugation, and stability studies to confirm the stability of the system. The mean particle size and size distribution of emulsion globules was determined by using photon correlation spectroscopy using Zeta sizer (Nano ZS 90, HORIBA, JAPAN). The dispersed formulations were measured after dilution (1:100) to produce the required count rate (50-200). The zeta potential of formulations was determined using Zeta sizer (Nano ZS 90, HORIBA, JAPAN). Charge on emulsion droplets and their mean Zeta potential values (±SD) were obtained from the instruments.

For Fenofibrate, the mean particle size of the formulation SNE16, containing Meglyoil as oil, PEG400 as co-surfactant and Tween80 as surfactant (i.e in 1:1 ratio) found to be 45.49 nm. decrease in the droplet size might be the result of more surfactant being available to stabilize the oil-water interface. Furthermore, the decrease in the droplet size reflects the formation of a better close-packed film of surfactant at the oil-water interface, there by stabilizing the oil droplets.

For Simvastatin, the mean particle size of the formulation SNE15, containing Oleic acid as oil, Transcutol-p as co-surfactant and Cremophore RH-40 as surfactant (i.e in 1:1 ratio) found to be 60.1 nm. such as decrease in the droplet size might be the result of more surfactant being available to stabilize the oil-water interface. Furthermore, the decrease in the droplet size reflects the formation of a better close-packed film of surfactant at the oil-water interface, there by stabilizing the oil droplets.

The viscosity of nanoemulsion formulation generally was very low. This was expected, because one of characteristics of nanoemulsion formulation is lower viscosity.

The viscosity of formulation was determined without dilution using BROOKFIELD-DV-II+pro viscometer using spindle 00 UV adaptor at 25+_0.5 °C. The viscosity of the optimized formulations was determined. It was observed that the viscosity of all the formulations is less than 170 cP. Formulation SNE16 has the minimum viscosity (104.68 cP) which is highly significant as compared to the other formulations for simvastatin. It was observed that the viscosity of all the formulations is less than 50 cP.
Formulation, SNE15 has the minimum viscosity (23.1 cP) which is highly significant as compared to the other formulations.

Electrical conductivity of the formulations was determined to check the stability and assert the nature of the formulation. It was found that the conductivity was the lowest (12.43 ± 0.62 mS/cm) in SNE1 and highest (22.89 ± 0.23 mS/cm) in SNE16 formulation. The higher conductivity of SNE16 is attributed to a larger percentage of water which allows more freedom for mobility of ions. Electrical conductivity of the formulations was determined (Table 25) to check the stability and assert the nature of the formulation. It was found that the conductivity was the highest (17.035 ± 0.5 mS/cm) in SNE1 and highest (32.047 ± 0.5 mS/cm) in SNE15 formulation.

There were no interaction between nanoemulsion excipients and drug. Refractive index of selected formulations was determined using an Abbe type refractrometer. It is also used as a parameter in the determination of droplet size distribution of nanoemulsion as the droplet size measurement is done by light scattering observed at 90° angle. The refractive index of all selected formulations was in the range of 1.39 to 1.41. Refractive index of selected formulations was determined using an Abbe type refractrometer. It is also used as a parameter in the determination of droplet size distribution of nanoemulsion. For simvastatin, the refractive index of all selected formulations was in the range of 1.75 to 1.95.

Examining the surface of a polymeric drug delivery system can provide vital information on the porosity and microstructure of these systems. The distribution and morphology of the surface and the encapsulated matrix can also be directly observed. For both formulations, particle size range were in between 100-200 nm.

Dissolution studies of samples were performed according to USP type-II apparatus in Phosphate buffer pH 7.4 respectively. The temperature was maintained at 37±0.5°C and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed by RP-HPLC. And it was found that the optimized formulations exhibits highest dissolution rate and in-vitro permeability.
Dissolution studies were performed to compare the release of drug from five different nanoemulsion formulations (SNE1, SNE12, SNE15, SNE16, SNE20), and conventional capsule formulation having same quantity (50 mg) of Fenofibrate. Interesting result was that the release from SNE1, SNE15, SNE20, SNE12 was significantly less than SNE16 (i.e., 99.67%) was obtained in case of this is because of small globule size, and eventually higher surface area in case of nanoemulsions, which permit faster rate of drug release.

Dissolution studies were performed to compare the release of drug from five different nanoemulsion formulations (SNE1, SNE3, SNE5, SNE9, SNE15), and conventional capsule formulation having same quantity (10 mg) of simvastatin. Interesting result was that the release from SNE1, SNE3, SNE5, SNE9 was significantly less than SNE15 (i.e., 99.94%) was obtained in case of this is because of small globule size, and eventually higher surface area in case of nanoemulsions, which permit faster rate of drug release.

By the Bio-equivalence study of optimised formulations and marketed formulation of simvastatin (tablet) and fenofibrate (capsule) it was found optimised formulations were found to be exhibits high bioavailability than marketed formulation.

The bio-equivalence studies for marketed capsule and nanoemulsion was determined in USP dissolution medium pH 7.4. At the end of 45 min, the dissolution of the fenofibrate from the SNE16 was significantly greater (99.67%) than that for marketed capsule (49.67%). This may be the result of surfactant molecules which leads to the enhancement of solubility of the drug in dissolution medium. This conclusion compares favorably with earlier study showed that the drug associated with SNEDDS and better results were found.

The bio-equivalence studies for marketed tablet (simvas10mg) and nanoemulsion was determined in USP dissolution medium pH 7.4. The results are shown in Figure. At the end of 1 h, the dissolution of the simvastatin from the SNEDDS was significantly greater (99.94%) than that for marketed tablet (49.45%).
may be the result of surfactant molecules which leads to the enhancement of solubility of the drug in dissolution medium. This conclusion compares favorably with earlier study showed that the drug associated with SNEDDS and better results were found.

1 mg/ml solutions of optimized formulations and marketed formulations were prepared in to suspension and filled into the rat duodenum, and permeation studies were performed in phosphate buffer pH 5.5. The samples were collected at regular intervals and analyzed by RP-HPLC. It was evident from the in vitro dissolution data of samples, that the optimized formulations exhibited a faster dissolution rate as compared to the marketed formulations with complete drug release in 1 hour.

The in-vitro intestinal permeability results exhibits the drug diffused at a faster rate from the SNEDDS system than from the tablet dosage form. After 1 hour of diffusion, 75.45% of drug was diffused from the SNEDDS system, as compared with 33.38% diffused from the tablets.

The drug concentration was determined by High performance liquid chromatography at maximum wavelength 238nm and the percent diffusion of drug was calculated against time and plotted on a graph.

The in-vitro intestinal permeability results exhibits the drug diffused at a faster rate from the SNEDDS system than from the tablet dosage form. After 1 hour of diffusion, 79.32% of drug was diffused from the SNEDDS system, as compared with 34.23% diffused from the tablets.

Hypolipidemic activity of Simvastatin causes reduction in elevated total CH, LDL-CH and TG levels in blood. On comparison with plain simvastatin, optimized nanoemulsion formulation (NESIM) , (NE15) shows better results indicates that plain simvastatin lowered cholesterol, triglyceride, LDL . It was observed from present study that nano particle formulation of simvastation were found to effect the serum lipids by Total cholesterol, Triglycerides and LDL .

Among the formulations tested, a significant improvement inthe rate and extent of absorption was observed for the nano emulsion formulations. Overall a two- to fivefold improvement in the relative bioavailability (RA) deduces the potential of nanoemulsion as a suitable carrier for improved oral delivery of fenufibrate.
➢ By observing the results we can conclude that selection of suitable oil, surfactant and co-surfactant, plays a vital role in the self emulsifying systems. Pseudo ternary phase diagrams construction will depend on ratios of surfactant and co-surfactant, and this leads to observe the formation of emulsion region.

➢ We can also conclude that ratio of surfactant and co-surfactant also affects the stability of emulsions, as they interfere with the interfacial film of the two phases.

➢ From the results we can observe that higher dissolution rates for both Simvastatin and Fenofibrate formulations as compared to their marketed preparations, and also higher permeability (diffusion) rate as compared to the marketed formulations. These are due to the more available surface area of particles, when they are prepared in nano formulations.
FUTURE RECOMMENDATIONS:

- The high surfactant level typically present in SNEDDS formulation can lead to GI side effects and a new class of super saturable formulations including super saturable SNEDDS (S-SNEDDS) formulations have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs.

- SNEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules).