Available online at http://jddtonline.info

RESEARCH ARTICLE

SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) FOR ORAL DELIVERY OF ATORVASTATIN- FORMULATION AND BIOAVAILABILITY STUDIES

Venkatesh Miryala, **Mallesh Kurakula***

Department of Pharmaceutics, Lalitha college of Pharmacy, Venkatapur, Ghatkesar,

R.R district, Andhra Pradesh, INDIA

Address for Correspondence: *Mallesh Kurakula, Masters in Pharmacy, Department of pharmaceutics, lalitha college of pharmacy, Hyderabad, India.Phone: 91 9550645635, Email:mallesh_kurakula@yahoo.com.*

ABSTRACT:

The aim of the study was to develop a self-nano emulsifying drug delivery system (SNEDDS) for the atorvastatin which belongs to BCS class II lipid lowering agent with poor water solubility and dissolution rate. The solubility of atorvastatin in individual micro emulsion components viz. oil and surfactants was determined. The surfactants were screened for emulsification ability. Based on the solubility determinations and emulsification properties oleic acid as oil; surfactants Brij 80 and Tween 80 were selected for further study. The solubility of atorvastatin in different ratios of selected oil and surfactants was determined. The composition of oil: Surfactant with maximum solubility for atorvastatin was used for SNEDDS formulation. Ternary phase diagrams were used to evaluate the micro emulsification existence area. The micro emulsions were evaluated for emulsion droplet size, self-emulsification time, phase separation, *in vitro* dissolution and stability. SNEDDS formulations found to be self-emulsified in 70 to 120 seconds without precipitation and their mean droplet sizes was 150 to 230 nm. Among the optimized formulations, formulation BF4 showed highest *in vitro* drug release. Formulation BF4 was composed of 20% oleic acid, 60% tween 80 and 20% brij 30 showed significant increases in the dissolution rate (99.65%) in 90 minutes and intestinal absorption (86.67%) than marketed product with 56.86% release and 45.34% oral absorption. Stability studies were conducted according to the Q1 ICH guidelines and found stable at different conditions.

Key words: - Self-nano emulsifying drug delivery system, Atorvastatin, Hypercholestermia, Tween 80, Brij 30.

INTRODUCTION:-

Majority of drugs are frequently administered through oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is complicated for the reason that of their low bioavailability, high intra- and inter-subject variability, and not have dose linearity[1,2]. To overcome these problems, a variety of strategies have been developed including the use of surfactants[3], lipids[4], permeation enhancers[4], micronization[5], salt formation[6], cyclodextrins[7], nanoparticles and solid dispersions[4,5] etc. There has been emergent attention in the use of lipid excipients in self-emulsifying lipid formulations (SELFs) for the reason that of their capability to solubilize poorly water-soluble 'lipophilic' drugs and prevail over the problem of poor drug absorption and bioavailability[8].

Micro emulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self- emulsifying systems[8]. Non-ionic surfactants, such as Tweens (polysorbates) and labrafil (poly-oxy-ethylated oleic glycerides), with high hydrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production[9].

Amphiphilic, non-ionic surfactants allow higher degrees of drug solubilisation to occur and may prevent the precipitation of drug out of the micro-emulsion *in vivo*. Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30 per cent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol[10]. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hydroscopic contents from dehydrating or migrating into the capsule shell[11].

Atorvastatin, as a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methyl- glutaryl-coenzyme A (HMG CoA) reductase which catalyzes the conversion of HMG-Co A to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia. It is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and pH 7.4 phosphate buffer. The intestinal permeability of atorvastatin is high at the physiologically relevant intestinal pH. However, it is reported that the absolute bioavailability (*F*) of atorvastatin is 12% after a 40 mg oral dose[12]. In present study SMEDDS of Atorvastatin was prepared for enhanced solubility and dissolution of poorly soluble drug.

MATERIALS AND METHODS:

Atorvastatin calcium (API), soybean oil, sunflower oil and olive oil obtained as a gift sample from Bright Labs, Hyderabad. Brij 30, Acetonitrile (HPLC grade), potassium dihydrogen phosphate, Ortho phosphoric acid (AR grade)

were procured from Qualigens Ltd., Mumbai. Tween 80, oleic acid, PEG 400, methanol (AR grade) were procured from S.D Fine chemicals, Mumbai. HPLC grade water was obtained from SD-Lab star (3TWF-UV) water purification system.

Solubility Studies:

To quantify and understand the solubility studies of atorvastatin an analytical method using RP-HPLC (Shimadzu Prominence LC-20AD was developed, optimized and validated. The solubility of atorvastatin calcium in various oils (soybean, sunflower & olive), surfactant and co-surfactants was measured using vial shake method. Unknown amount of selected vehicles was added to each cap vial containing an excess of atorvastatin , heated up to 40^{o}C and centrifuged (Remi RM-12C centrifuge) at 3000 rpm for 5 min. Excess insoluble atorvastatin was discarded by filtration using a membrane filter (0.45 µm, 13 mm). The concentration of atorvastatin was then quantified by RP-HPLC method (Shimadzu Prominence LC-20AD). Solubility study was performed at triplicate and standard deviation was calculated.

Preliminary screening of surfactants:-

Different surfactants for the per oral use were screened for emulsification ability. Briefly, 150 mg of each surfactant was added to 150 mg of the oily phase, heated up to 50^{0}C and diluted to 100 ml with water. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2 hours and their percentage transmittance was evaluated by UV-Visible spectrophotometer[13] (Shimadzu, Japan). Emulsions were furthermore observed visually for any turbidity or phase separation. The selected oily phase and surfactant were used for further screening of the different co-surfactants (Brij 30 and tween 80) for their emulsification ability.

Construction of Ternary phase diagram:

The ability of oil within surfactant: co-surfactant that could self-emulsify under proper dilution can be identified and selected from ternary phase diagrams. Ternary phase diagram were constructed using water titration method. The mixture of oil with surfactant or combination of surfactant and co-surfactant were prepared in different ratios, titrated against water and agitated (Remi CM 101 DX) until slightly bluish emulsion was formed. Percentage of oil, surfactant: co-surfactant mixture and water was calculated using ternary phase diagram. CHEMEX 3.51 software tool was used to find out the emulsification zone[14]. Further the same procedure was repeated instead of oil surfactant mix to determine the effect of drug on phase diagram.

Formulation of SNEDDS:

10 mg of atorvastatin was dissolved in co-surfactant at 45˚C in an isothermal water bath. After cooling, calculated amount oil and surfactant was added and sonicated (Citizen Digital, India) until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 hours to examine the signs of turbidity or phase separation. Formulations made were examined for leakage by filling in hard gelatin capsules[15].

Table1. Various Formulations using oil: co-surfactant/surfactant ratio

Formulation code	Drug (mg)	% Oleic acid	% Tween 80	% Brij 30
BF1	10	5	47.5	47.5
BF2	10	5	63.33	31.66
BF3	10	10	45	45
BF4	**10**	**10**	**60**	**30**
BF5	10	15	42.5	42.5
BF6	10	20	56.66	28.33
BF7	10	20	40	40
BF8	10	25	53.33	26.66
BF9	10	25	37.5	37.5
BF10	10	25	50	25
BF11	10	30	35	35
BF12	10	30	46.66	46.66
BF13	10	35	32.5	32.5
BF14	10	35	43.33	21.66
BF15	10	40	30	30
BF16	10	40	40	20
BF17	10	45	27.5	27.5
BF18	10	45	36.66	18.33
BF19	10	50	25	25
BF20	10	50	33.33	16.66

Characterization:

1. Determination of self -emulsification time:

The primary means of self-emulsification assessment is by visual evaluation. The efficiency of self-nano-emulsification is estimated by agitation at 100 rpm in mixture of water and 0.1N HCl solution (100ml) at temperature 37ºC[15]. The time required to form nano-emulsion depends upon dilution of SNEDDS with water.

2. Visual observation, Phase separation and stability study of emulsion:

Different formulations were diluted, agitated with 20ml of distilled water at 37˚C and allowed to stand for 24 hours. Further visual observation was made to check the

 ISSN: 2250-1177 CODEN (USA): JDDTAO

extent of phase separation and precipitation. Mixtures exhibiting a negligible phase separation during the 24 hour period were selected for further studies and evaluated on visibility grades[16].

Table- 2 Visibility grades

Grade	Dispersibility and appearances
I	Clear or slightly bluish in appearance
II	Bluish white appearance.
III	Bright white emulsion (similar to milk
IV	Dull, grayish white emulsion with a slightly oily appearance
V	Turbid appearance

3. Droplet size, Zeta potential and poly-dispersity analysis:

The mean droplet size, zeta potential and poly-dispersity index of formulations was determined by using Zeta seizer HAS 3000 (Malvern Instruments Ltd., Malvern, UK). Light scattering was monitored at 25°C at a 90° angle[16]. The dispersed formulations were measured after dilutions (1:100).

4. FTIR studies:

Infrared (IR) spectroscopy studies were conducted using FTIR (Bruker Alpha T, Germany) at 4000 to 500 cm^{-1}. Liquid sample preparations were made as per the instrument and the spectrum was recorded for various formulations[17].

5. Physical analysis:

The surface morphology, roundness, formation of aggregates and size distribution of nano globules formed were studied by Scanning Electron Microscopy (Model: JSM-5510Jeol Ltd, Tokyo, Japan). 1gm of formulation was diluted with 10ml of pH 6.8 phosphate buffer. The nano-emulsions were mounted on an aluminum stub using double-sided carbon adhesive tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator and examined with digital camera, at 20kV accelerating voltage[17].

6. Drug content:

Various formulations equivalent to 10 mg were taken into a standard volumetric flask, mixed and diluted with methanol. 1 ml of this solution was diluted to 10 ml with phosphate buffer pH 6.8; it gives 100µg/ml (theoretical). Further drug content was quantified using RP-HPLC method developed at 246 nm.

$$\%\ of\ drug = \frac{standard\ peak\ area}{sample\ peak\ area} \times 100$$

Standard peak area at 100µg/ml

7. Cloud point measurement:

Formulations were diluted with 50 ml of water and placed on a water bath with gradually increase the temperature until the diluted formulation turned to cloudy. It gives the information about the stability of the nano-emulsion at body temperature[18].

8. In *vitro* release study:

Quantitative *in vitro* release test was performed using USP XXIV method (dissolution apparatus #2, at 50 rpm) in 900 ml 0.05M phosphate buffer at pH 6.8. SNEDDS (equivalent to 10 mg) was placed in dialysis bag to compare the release profile with conventional tablets[19]. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, dilute suitably and analyzed chromatographically (RP-HPLC). Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage cumulative drug released at different time intervals was calculated and graph plotted versus time.

9. *In vitro* rat intestinal permeability study:

Various methods employed for intestinal permeability were modified within experimental procedures described in the literature. Male albino rats (250-300 grams) were killed by overdose with pentobarbitone IV injection. To check the intra-ileum permeability, the ileum part of intestine was isolated, washed thoroughly with cold Ringer's solution to remove the mucous and lumen contents. The formulations were diluted with 1 ml of distilled water and sample (1 mg/mL) was injected into the ileum using a syringe, making sure two sides of the intestine are tightly closed. The tissue was placed in a chamber of organ bath with continuous aeration at 37°C. The receiver compartment was filled with 30 ml of 0.05M phosphate-buffered saline (pH 6.8). At predetermined time intervals of 15, 45, 75,105,135 and 165 minutes (up to 2.75 hours), 2 ml of the samples were withdrawn and the drug concentration was determined by validated HPLC method[20]. Percentage cumulative drug absorption of drug was calculated by plotting the graph versus time. The same procedure was repeated for marketed tablet.

10. Thermodynamic Stability Studies:

1. Freeze–thaw cycle:

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at –4°C for 48 hours followed by thawing at 40°C for 48 hours. Centrifugation was performed at 3000 rpm for 5 minutes[21]. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

2. Stability Studies:

The hard gelatin capsules (size 0) filled with different formulation was placed in stability chambers (REMI, India). Stability studies at 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH were conducted according to ICH guidelines. Sampling was done at specified intervals over a period of 3 months for intermediate and accelerated conditions and 6 months for long-term conditions[21]. Drug content of the capsules was analyzed using developed RP-HPLC method.

RESULTS AND DISCUSSION:

Solubility studies:

Table 3 Solubility of Atorvastatin in various oils, surfactants and co-surfactants

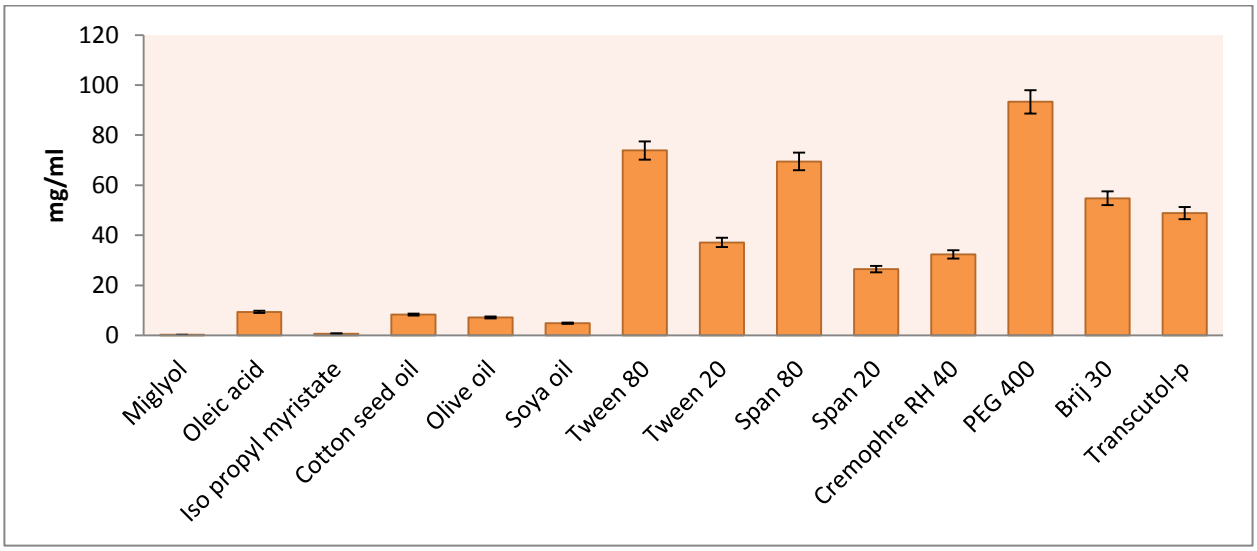
SNO	Vehicle	Solubility in mg/ml
1	Miglyol	0.33
2	**Oleic acid**	**9.4**
3	Iso propyl myristate	0.73
4	Cotton seed oil olive oil	8.36
5	Olive oil	7.21
6	Soya oil	4.89
7	**Tween 80**	**73.87**
8	Tween 20	37.14
9	Span 80	69.5
10	Span 20	26.5
11	Cremophore RH 40	32.4
12	PEG 400	93.3
13	**Brij 30**	**54.8**
14	Transcutol-p	48.9

Selection of right component is important prerequisite for formulation of stable SNEDDS. The drug should have good solubility in components of micro emulsion so as the precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. Therefore, the solubility of atorvastatin calcium was determined in various oils, surfactants and co-surfactant mixtures. The solubility results are depicted in figure I. Among the various components studied oleic acid, Brij 30 and Tween 80 showed maximum solubility 9.8 ± 1.79, 73.87 ± 1.73 and 54.83 ± 0.51 mg/ml respectively. The solubility results for oil: surfactant mixtures are showed in Table 3.

As the solubility of atorvastatin was maximum in oleic acid, Brij 30 and Tween 80 these were selected as oil and surfactant component for further development of SNEDDS. Final selection among different components would secondly be confirmed according to emulsification properties with other ingredients. Regarding surfactants and co-surfactants selection, drug solubility would come second to the main selection perspective: emulsification efficiency.

Tween 80 a non-ionic surfactant with high HLB value 15, which has miscible with atorvastatin, being less toxic and less affected by pH and ionic changes in the dispersion medium. Oleic acid was selected as oily phase because it has ability of high spontaneity for emulsification and high drug loading capacity. Brij 30 (HLB-9) was selected as co-surfactant it is a medium chain mono glyceride promotes water penetration and has good solvent capacity for drugs.

Figure-1 Solubility of atorvastatin in various oils, surfactants and co-surfactants



Phase diagram

Figure 2 and 3 represents the phase diagrams of oil-surfactant-water systems: (oleic acid, Tween 20: Brij 30 and water) in different ratios. These phase diagrams showed the different areas of bluish nano emulsion (NE), slightly bluish micro emulsion (ME), and coarse emulsions (ME). It can be seen that the largest micro emulsion region

is seen when the combination of surfactant and co-surfactant are used.

Ternary phase diagrams were constructed to identify the self-emulsifying regions and also to establish the optimum concentrations of oil, surfactant and co-surfactant. From the phase diagrams, it was observed that as increasing the concentration of surfactant increased the self-emulsifying region. Emulsification region decreased with increasing the concentration of co-surfactant. Efficiency of self-emulsification was good when the surfactant concentration was more than 50%. From the formulations as the concentrations of oil increases (above 35%) showed the phase separation of SNEDDS formulation. Effect of drug on phase diagram study was conducted to check the effect of emulsification region and stability of the emulsification process. Emulsification zone was narrowed as the concentration of drug increased, viscosity of the system is increased and some formulations showed gel like appearance. BF8, BF10 showed increase in the viscosity. BF16, BF18 and BF20 very viscous emulsions because the concentration of oil and surfactant concentration increases the viscosity y of the system increased, transparent emulsion was formed with increase in the concentration of concentration of Brij 30.

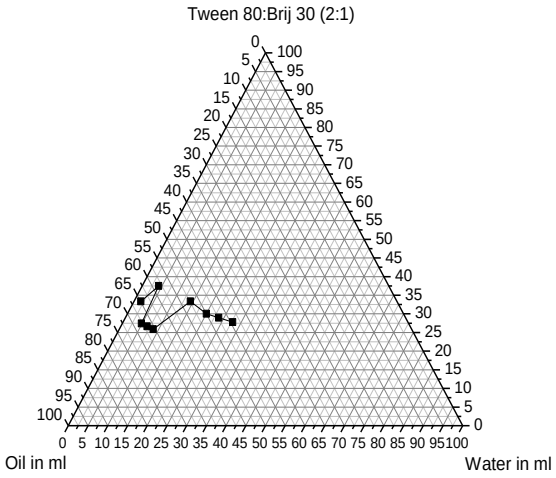


Figure 2- 2:1 ratio

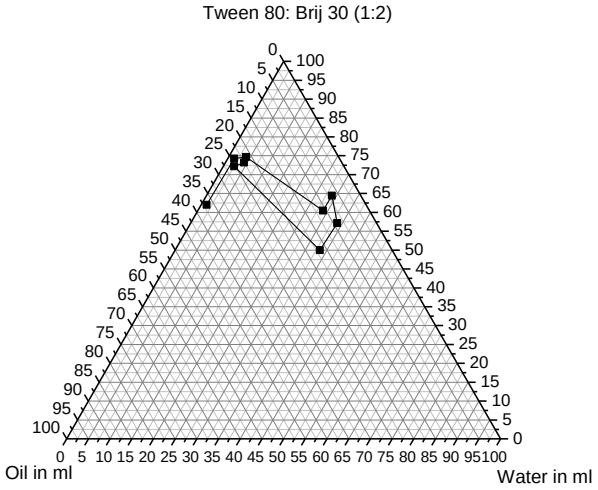


Figure 3- 1:2 ratio

Characterization:

1. **Visible Assessment, Phase separation and Stability study:**

Formulations BF1 to BF11 showed no crystal growth or no precipitation which formed micro emulsion upon dilution and was stable for 24 hours. The remaining formulations showed phase separation and precipitation. It indicates that as concentration of oil increases the stability of formulation is decreased and also increase in surfactant content the clarity is better.

Table 4. Visible assessment SNEDDS after dilution and phase separation, precipitation results on storage

Formulation code	Visibility grade	Phase separation	Precipitation
BF1	II	X	XX
BF2	I	X	XX
BF3	II	X	XX
BF4	I	X	XX
BF5	II	X	XX
BF6	II	X	XX
BF7	II	X	XX
BF8	II	X	XX
BF9	III	X	XX
BF10	IV	X	XX
BF11	III	X	XX
BF12	IV	+	XX
BF13	V	+	++
BF14	V	+	++
BF15	V	+	++
BF16	V	+	++
BF17	V	+	++
BF18	V	+	++
BF19	V	+	++
BF20	V	+	++

X-- No phase separation, XX--No precipitation, +--phase separation and ++--precipitation.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

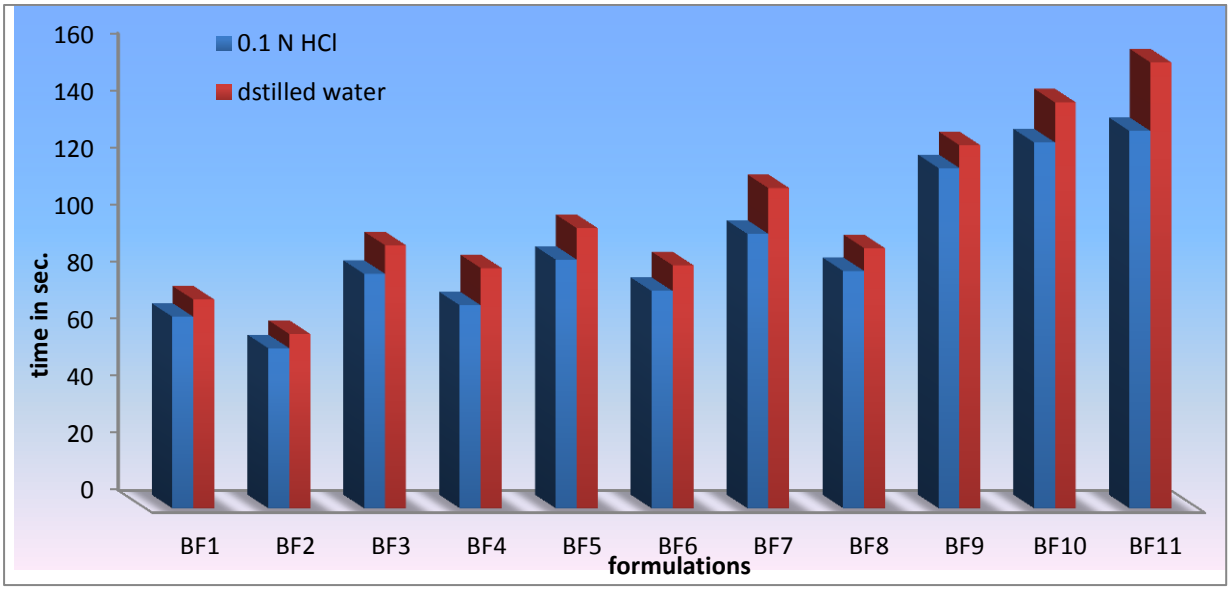
2. Determination of Emulsification Time:

In the study formulations (BF1-BF11) have shown spontaneity of emulsification and good stability without any signs of drug or excipient precipitation.

Table 5. Emulsification times of various SNEDDS formulations in 0.1N HCl and distilled water.

Formulation code	0.1N HCl		Distill water	
	Emulsification time (sec)	Tendency for emulsification	Emulsification time (sec)	Tendency for emulsification
BF1	67	good	73	good
BF2	56	good	61	good
BF3	82	good	92	good
BF4	71	good	84	good
BF5	87	good	98	good
BF6	76	good	85	good
BF7	96	good	112	bad
BF8	83	good	91	good
BF9	119	good	127	bad
BF10	128	good	142	bad
BF11	132	good	156	bad

Figure -2 Emulsification times of various formulations in 0.1N HCl & distilled water



3. Droplet size measurements:

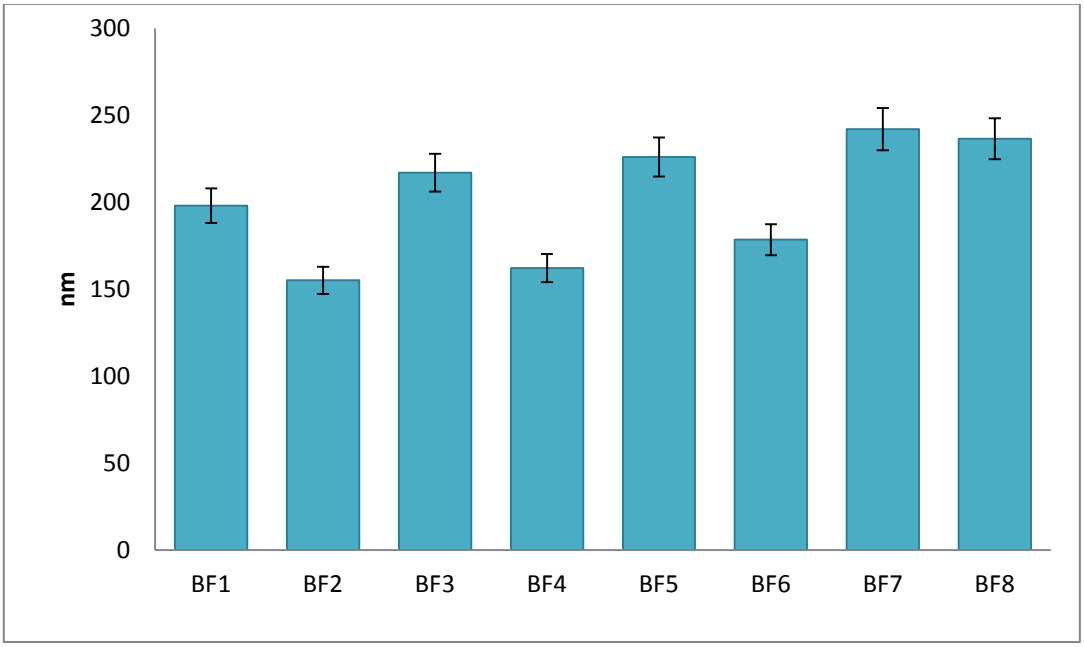
From the results, as the concentration of brij 30 increases uniformity of the nano emulsion decreased. Further characterizations were carried with formulations BF1, BF2, BF4 and BF6.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 6. Droplet size, PDI of the SNEDDS formulations

Formulation code	Droplet size (nm)	Poly Dispersity Index
BF1	198	0.282
BF2	155.1	0.179
BF3	217	0.412
BF4	162.2	0.297
BF5	226	0.415
BF6	178.5	0.315
BF7	242	0.556
BF8	236.5	0.489

Figure 3. Droplet size of nano emulsion



4. Zeta potential measurement:

Zeta potential of all SNEDDS formulation was in range of –17 to –30 mV in the 50 times dilution. SNEDDS formulations consist of non-ionic components and oleic acid which show relatively negative charge. Formulations BF4 and BF6 have surface charge more than 25mv meaning will not be affected by cell membrane charge during absorption and also can produce stable nano emulsion particles. The results were similar of phenytoin.

Table 7. Zeta potential of formulations

Formulation code	Zeta potential (mv)
BF1	-16±4.35
BF2	-18±5.65
BF4	-24.6±6.47
BF6	-28±5.84

4. Cloud point measurement:

Cloud points of all formulations were very high about 80˚C. In all formulations, cloudiness was reversible after few minutes. Phase separation, precipitation occurred possible due to dehydration of POE moiety, alkyl chains of surfactant system .

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 8. Cloud point of stable SNEDDS formulation

Formulation code	Cloud point
BF1	74±6.52
BF2	73±5.15
BF4	80±4.64
BF6	76±5.8

5. Thermodynamic stability study:

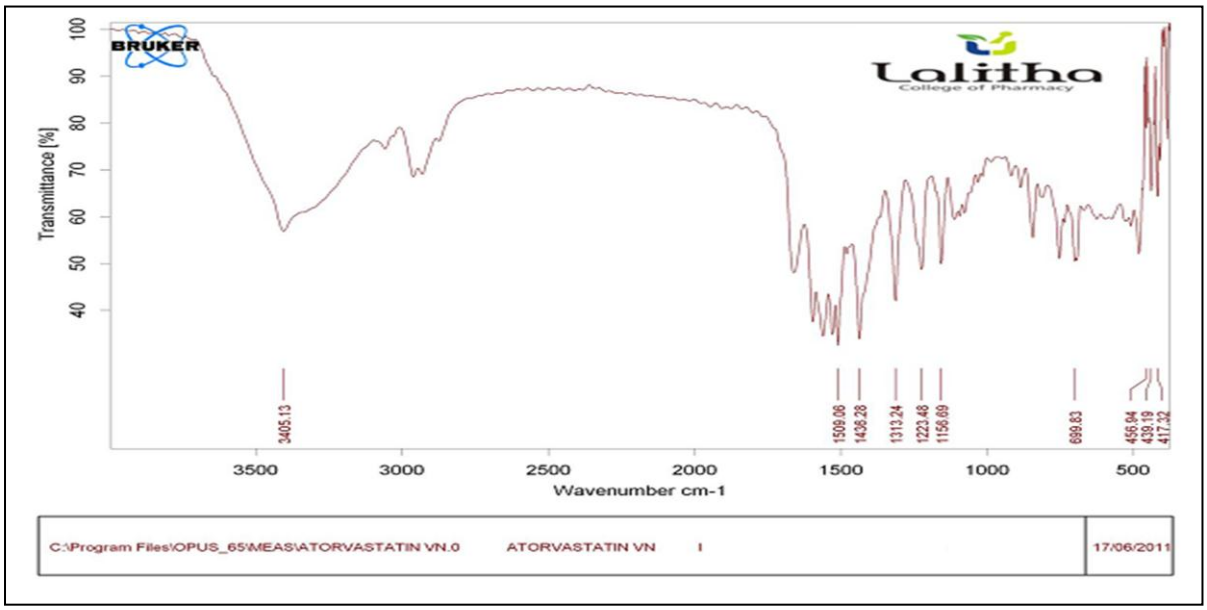
Thermodynamic stability study was designed to identify and avoid the metastable formulations.

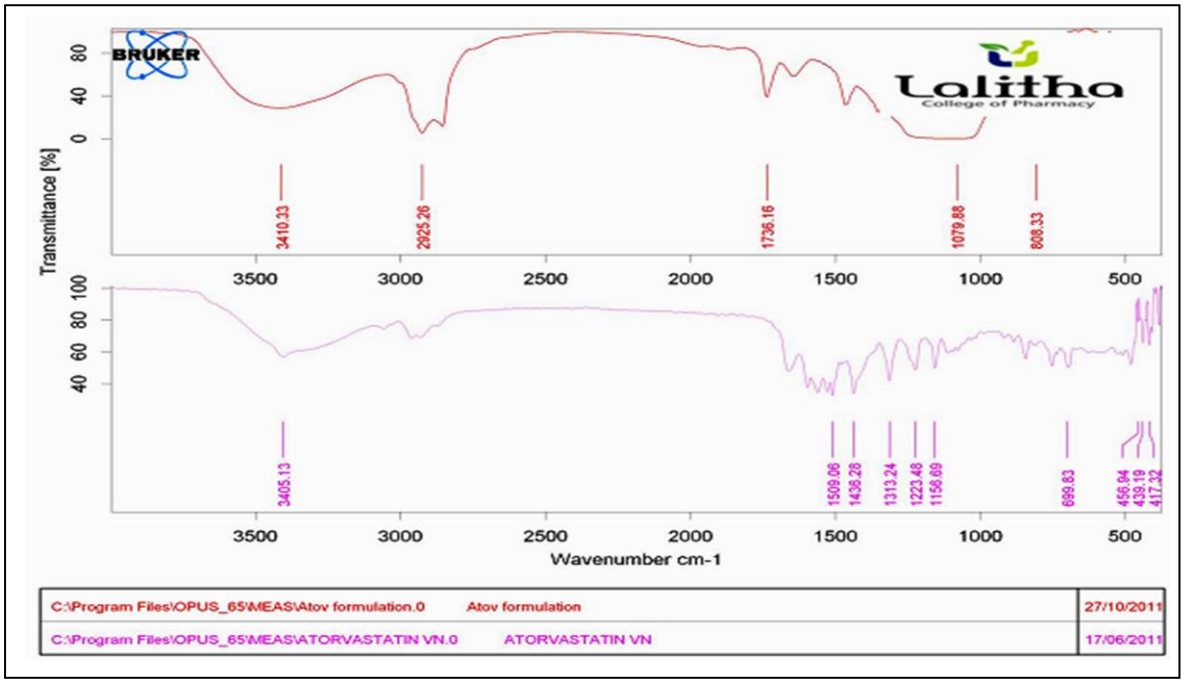
The formulations were stable during centrifugation at 3500 rpm at alternative temperature cycles of 40˚c and -4˚c. There was no phase separation and precipitation observed.

6. FTIR Studies:

From the spectra, it is observed there is possibility of intermolecular hydrogen bonding between adjunct atorvastatin molecules. The spectrum of pure atorvastatin was equivalent to the spectra obtained by the SNEDDS indicating there were no possible incompatibilities.

Figure 4 IR spectra of pure atorvastatin

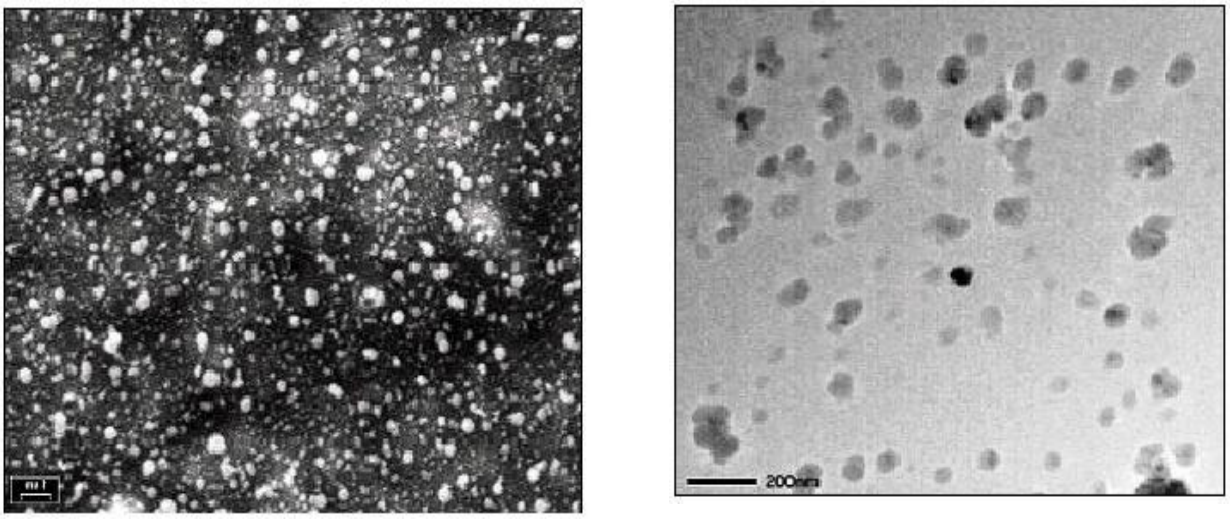




7. Physical Analysis of globules:

Scanning electron micrographs revealed the formation of well identified spherical globules with sharp boundaries after hydration, similar to those seen with lutein loaded novel SNEDDS. The surface characteristics of SNEDDS-derived nano emulsion are depicted in the figure 6.

Figure 6 (a) SEM at 1µm (b) SEM at 200nm



8. Drug content:

The drug content for the selected formulation was calculated using the standard formula.

Table 9 Percentage of drug in various formulations

Formulation code	Percentage of drug
BF1	99.52
BF2	98.42
BF4	99.67
BF6	99.33

9. *In-vitro* release studies:

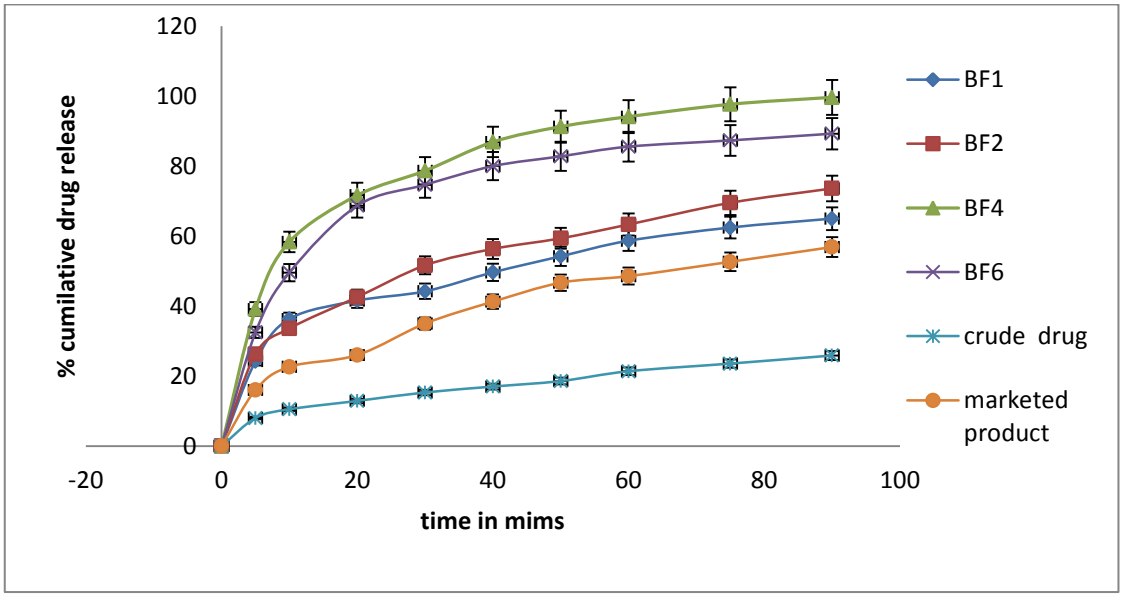
The percent cumulative release of Atorvastatin from the formulations BF4 and BF6 was found to be higher than the other formulations and marketed product (storvas® 10 mg). The percentage drug released after 90 minutes for BF4 and BF6 were 99.65% and 89.26% were as 56.86% release for marketed product. Cumulative percent drug release is high in formulation BF4 because of low viscosity and high concentration of surfactant i.e. Tween 80.

Table 10. Cumulative percent release of Atorvastatin from various formulations

Time(min)	BF1	BF2	BF4	BF6	crude drug	marketed product
0	0	0	0	0	0	0
5	24.24	26.28	39.12	32.46	8	16
10	36.33	33.59	58.34	49.56	10.5	22.64
20	41.54	42.56	71.65	68.67	12.88	26
30	44.21	51.62	78.66	74.65	15.3	34.99
40	49.63	56.31	86.89	79.98	16.98	41.24
50	54.21	59.35	91.26	82.78	18.56	46.66
60	58.66	63.3	94.12	85.55	21.36	48.54
75	62.43	69.5	97.66	87.33	23.55	52.64
90	64.99	73.6	99.65	89.26	25.86	56.86

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Figure 7 Percentage cumulative drug release of various formulations.



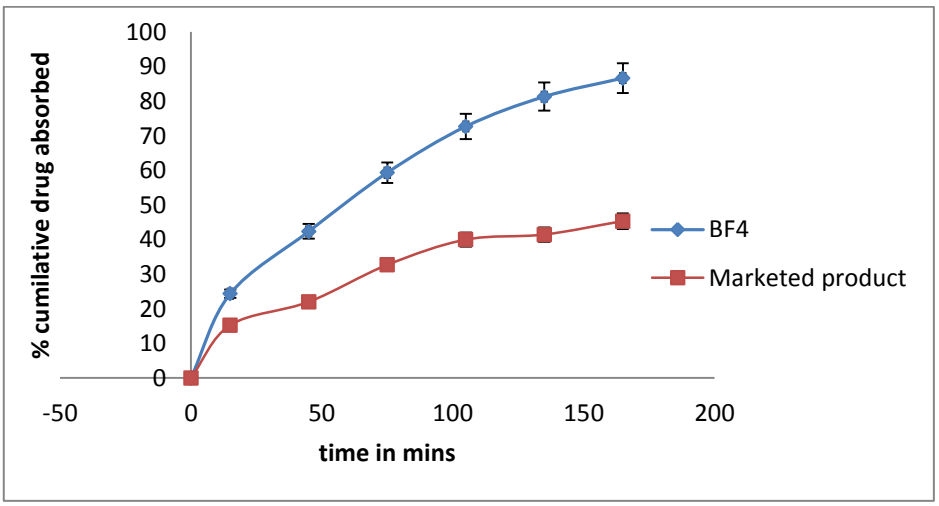
10. *In vitro* rat intestinal permeability study:

From the results it was observed that formulation BF4 has shown highest oral absorption (86.67%) thorough intestine after 165 seconds when compared to marketed product (45.34%). This may suggest absorption of the drug through the intestine increases with decreasing droplet size.

Table11 Percent cumulative drug absorbed through the rat skin

Time (min)	BF4	Marketed product
0	0	0
15	24.35	15.25
45	42.35	21.99
75	59.33	32.68
105	72.69	39.98
135	81.31	41.45
165	86.67	45.34

Figure 8 Comparison of intestinal absorption between BF4 and marketed product



11. Stability studies:

The formulations BF4 and BF6 were found to be stable for 3 months and there was no significant change in the drug content, or particle size.

Table 12. Evaluation data of SNEDDS formulation subjected to stability studies at (25°c/60% RH)

Formulation code	Sampling point	Droplet size size(nm)	% drug content
BF6	0 days	178.5	99.33
	45 days	178.5	98.75
	3 months	179.5	97.98
BF4	0 days	162.2	99.67
	45 days	162	98.28
	3 months	165	97.51

Figure 9 Droplet sizes of the formulations after 3 months at 25°c/60% RH.

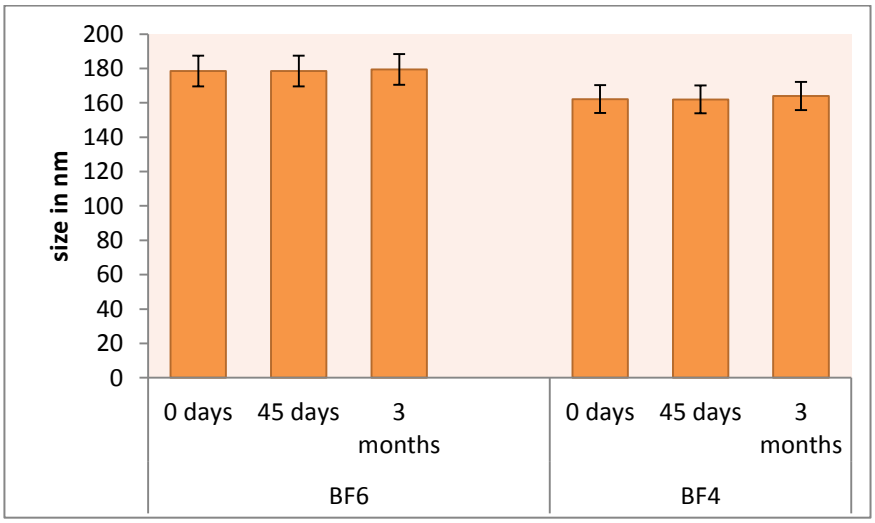
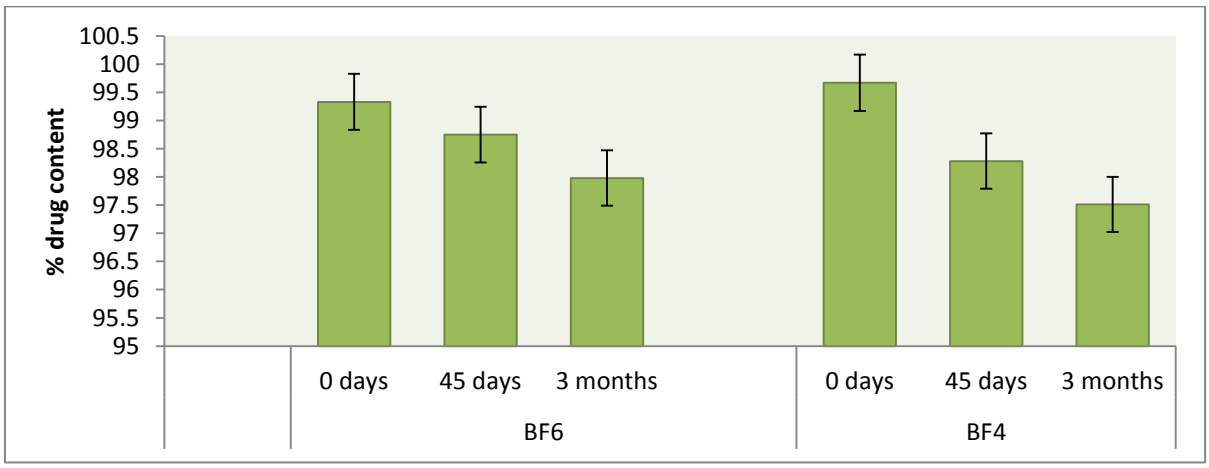


Figure 10 Drug content after storage at 25°c/60% RH



CONCLUSION:

An optimized atorvastatin loaded formulation consisting of oleic acid, Tween 80 and Brij 30 offers the advantage of good solubilisation of atorvastatin. Thus our studies confirmed that SNEDDS can be used as a possible alternative to conventional oral formulation of atorvastatin. Results further conclude that SNEDDS can be explored as a potential drug carrier for dissolution enhancement of atorvastatin and other insoluble drugs.

ACKNOWLEDGMENTS:-

The authors are thankful towards Bright labs, Hyderabad for atorvastatin gift sample. Also Dr. Prakash v diwan for project guidance and Dr. Rajeshwar Reddy, Chairman, Anurag group of institutions for providing facilities, infrastructure for carrying out research work.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

REFERENCES:

1. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. Int. J. Pharm. 27: 335-348 (1985).
2. Singh A., Chaurasiya A., Singh M., Upadhyay S., Mukherjee R., and Khar R., ExemestaneLoaded Self-Microemulsifying Drug Delivery System (SMEDDS): Development andOptimization AAPS PharmSciTech, Vol. 9, No. 2, (2008)628-634.
3. Robinson, J.R., 1996. Introduction: Semi-solid formulations for oral drug delivery. B. T.Gattefosse. 89, 11-13.
4. Yuksel, N., Karatas, A., Ozkan, Y., Savaser, A., Ozkan, SA., Baykara, T., 2003. Enhanced bioavailability of piroxicam using Gelucire 44/14 and labrasol: in vitro and in vivo evaluation.Eur. J. Pharm. Biopharm. 56, 453-459.
5. Charman, S.A., Charman, W.N., Rogge, M.C., Wilson, T.D., Pouton, C.W., 1992. Selfemulsifying drug delivery systems: formulation and biopharmaceutical evaluation of aninvestigational lipophilic compound. Pharm Res. 9, 87-93.
6. Li, P., Ghosh, A., Wagner, R.F., Krill, S., Joshi, Y.M., Serajuddin, A.T.M., 2005. Effect ofcombined use of nonionic surfactants on formation of oil in-water emulsions. Int. J. Pharm. 288,27-34.
7. Jeong-Soo Kim, Min-Soo Kim, Hee Jun Park, Shun-Ji Jin, Sibeum Lee and Sung-Joo Hwang, Physicochemical properties and bioavailability of amorphous Atorvastatin hemi- calcium using spray drying and SAS process, DOI:10.1016/j.ijpharm.2008.04.006.
8. Patil, P., Joshi, P., Paradkar, A., 2004. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. AAPS PharmSciTech. 5(3), E 42.
9.Kanga,K.B.Lee,S.J.Chona,K.S.Jeong,Y.S.,Yuk,H.S.Khanga,G, Development of Selfmicroemulsifying drug delivery systems for oral bioavailability enhancement of Simvastatin in Beagle Dogs Int.J.Pharm,(2004)274,6573
10.Subramanian, N., Ray, S., Ghosal, S., Bhandra, R., Moulik, S. P., (2004) Formulation design of Self-Microemulsifying drug delivery systems for improved oral bioavailability of Celecoxib, Bio, Pharm, Bull., 27(12),1993-1999.
11.Land, L. M., Li, P and Bummer , P. M., (2005), the influence of water content of triglyceride oils on the solubility of steroids, Pharm.Res.,21, No 2, 254-260.
12.Wei Wu, Yang Wang, Li Que Enhanced bioavailability of silymarin by selfmicroemulsifying drug delivery system European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 288–294 13. Nazzal, S., Nutan, M., Palamakula, A., Shah, R., Zaghloul, A.A., Khan, M.A., 2002. Optimization of self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int. J. Pharm. 240, 103-114.
14. Grove, M., Mullertz, A., Nielsen, J. L and Pedersen, G. P., (2006), Bioavailability of seocalcitol II: Development and characterization of self microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides, Eur. J.Pharm.Sci,28(3), 233-242.
15. Eman A., Albert AB, Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS), European journal of pharmaceutical sciences 35 (2008) 257–263.
16. Kim, J. Y., Young, S. K.,(2000), Enhanced absorption of Indomethacin after oral or rectal administration of Self emulsifying system containing Indomethacin torats, Int.J.Pharm,194, 81- 89. 17. Pouton, C.W., Charman, W.N., 1997. The potential of oily formulations for drug delivery to the gastro-intestinal tract. Adv. Drug Del. Rev. 25, 1-2.
18. Patil P. and Paradkar A., Porous Polystyrene Beads as Carriers for Self-Emulsifying System Containing Loratadine, AAPS PharmSciTech 2006; 7 (1) Article 28.
19. Yu, X. L., wang, T.J., Hussain, S.A., (2002), Evaluation of USP apparatus 3 for dissolution testing of immediate release products, AAPS Pharmsci., article 4(1).
20. Odeberg, J. M., Kaufmann, P., Kroon, K.G., and Hoglund P., (2003), Lipid drug delivery and rational formulation design for Lipophilic drugs with low oral bioavailability, applied to Cyclosporine, Eur. J.Pharm.Sci, 20, 375-382.
21. Patel A. and Vavia P. , Preparation and In Vivo Evaluation of SMEDDS (Self- Microemulsifying Drug Delivery System) Containing Fenofibrate, The AAPS Journal 2007; 9(3) Article 41.
22. Jing C., Bo Y., Yu Z., Weiwei Z., Houli L., Hongxiang L., Guangxi Z., Enhancement of oralabsorption of curcumin by self microemulsifying drug delivery systems, Int.J.Pharm, (2008),doi:10.1016/j.ijpharm.2008.12.0090

 ISSN: 2250-1177 CODEN (USA): JDDTAO