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Research Article

A NOVEL TECHNICAL DEVELOPMENT AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF SIMVASTATIN

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ABSTRACT

The research article includes self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of drugs. Simvastatin is poorly water soluble drug. Aim of present study was to develop novel dosage form of self-emulsifying drug delivery systems (SEDDS) of Simvastatin. Article deals that before the formulation of SEDDS, solubility study was performed on different exicipients, and exicipients are selected on the basis of solubility in simvastatin. From the solubility study, better solubility was seen in oleic acid (oil), tween80 (surfactant), PEG 200 (co-surfactant) and ethanol (co-solvent). No drug exicipients interaction was seen. Particle size was 100 to 300 nm. Drug release up to 96.75 % in 3.5 hrs and showed excellent stability. SEDDS Simvastatin oral formulations were prepared that provides excellent drug solubilization, drug stability in water and improved *in vitro* release of simvastatin.

Keywords: ethanol, oleic acid, PEG 200, self-emulsifying drug delivery system, simvastatin, tween 80.

INTRODUCTION

Simvastatin is chemically 2,2-Dimethylbutanoic acid (1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a–hexahydro–3,7–dimethyl–8-[2-[(2*R*,4*R*)-tetrahydro–4–hydroxy–6–oxo–2*H*-pyran–2–yl]ethyl]-1–naphthalenyl ester. Simvastatin is a hypolipidaemic drug have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atheroscelosis in hyperlipidaemic individuals.

The objectives of this study will be to develop to enhance the solubility and improving bioavailability of SEDDS of simvastatin to administer them through oral route resulting in increasing their clinical efficacy. To identify the drug Simvastatin as per the existing standard . To formulate the Self Emulsifying Drug Delivery System of Simvastatin with different surfactant: co-surfactant ratio. To evaluate the Self Emulsifying Drug Delivery System parameters. Conformation of the better formulation by subjecting to relevant parameters like percentage drug content etc.

METHODS

Materials and chemicals

Simvastatin is obtained as gift sample from Cipla Pharmaceutical Ltd, Pune. Polyethylene glycol-200 and tween80 was obtained from Loba Chemei pvt ltd. Mumbai . Hydrochloric acid, oleic acid was obtained from S.D. Fine Chem.Ltd. Boisar.

Preparation of standard solution

Preparation of standard curve in 7:3 Methanol : Phosphate buffer(PH-7.4)

100mg of simvastatin drug was accurately weighed in 100ml volumetric flask and dissolve it in 70ml of methanol, to this solution 30ml of phosphate buffer(7.4) is added (SS- A).

Preparation of working standards
From (SS- A) pipette out 10ml and make up the volume to 100ml with 7:3 ratio of methanol: phosphate buffer(7.4) (SS-B). From (SS-B) aliquots of 0.4ml, 0.6 ml, 0.8ml, 1ml, 1.2ml, 1.4ml and 1.6ml were pipette into 10ml volumetric flasks. The volume was made up with 7:3 ratio of methanol : phosphate buffer(7.4) to get the final concentration of 4,6,8,10,12,14,16 µg/ml respectively. The absorbance of each concentration was measured at 239 nm. A standard graph was drawn using the average values of seven trials by plotting absorbance versus concentration of Simvastatin.

Preparation of sample solution
100 mg of simvastatin was accurately weighed and dissolved in 100ml of ethanol (SS- I), from this solution pipette out 10ml and added to another 100ml volumetric flask.The volume was made up with methanol to get a concentration of 100µg/ml (SS-II).From (SS-II) pipette out 0.6ml into 10ml volumetric flask and make up the volume with methanol (SS-III).Ultraviolet scan was taken of (SS-III) between the wavelengths 200-400nm against methanol as the blank which gave a highest peak at 239nm and the same was selected as λ_{max} of Simvastatin.

Formulation design
This involves mixing of different oils, surfactant, co-surfactant and co-solvent First impastation was dissolved in ethanol by stirring. Then oleic acid was added slowly with stirring. Then appropriate amount of PEG-200 was added to Tween-80 and mixed properly by stirring with a glass rod. Then the mixture of Tween-80 and PEG-200 were added to the drug-ethanol solution and mixed by stirring. Formula for the preparation of self emulsifying drug delivery system of simvastatin table no:1

RESULTS AND DISCUSSION
IR Spectras
The sample of Simvastatin procured for study was identified by Infrared spectrum as shown in fig8, and the polymers do not interact with drug spectrum in all the formulations

Determination of λmax Of Simvastatin: As UV spectrophotometric method was selected for quality control purposes, the λ_{max} was found to be 239 nm from UV spectrum of Simvastatin in Methanol. From the data obtained it can be said that the drug follows the Beer's law in the concentration range of 4-16 mcg/ml.

Solubility of Simvastatin in Ethanol, Oleic acid, PEG-200 and Tween-80
The self-emulsifying formulations consisted of oil, surfactants, co-surfactants, and drug should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase, hence it should have good solvent properties to allow presentation of the drug in solution.

Phase Diagram Study
Pseudo-ternary phase diagrams were constructed to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant and co-surfactant.

Evaluation of SEDDS of Simvastatin
In-vitro Drug Diffusion Studies
The appearance of Simvastatin in the acceptor phase as a function of time was monitored from formulations in the dialysis membrane. It appears that the release of Simvastatin from the formulations containing the smallest amounts of drug (2 mg) is completed within 3-4 hrs. Interestingly, the initial release profile is higher, however, the release rate declined with the release being completed 96% after 3.5hrs.

Determination of % Drug content
S1 Formulation contained maximum drug and hence showed highest % drug content of 99.08.

Scanning Electron Microscopy
The photographic image of micro particles showing surface morphology under SEM is shown in fig no.25. From the SEM study the average particle size was found to be within 50 nm and the shape was found to be spherical.

Stability Study
Stability studies of the SEDDS samples were carried out by subjecting them to temperature stability. The temperature stability study was carried out by keeping the micro emulsion sample at two different temperatures (2–8˚C and room temperature) for two months and visual inspection was carried out by drawing samples at monthly intervals for the subsequent months. No evidence of phase separation or any flocculation or precipitation was observed in some SEDDS formulation.

Table 1: Ingredients for the preparation

Formulations	Drug (simvastatin) In mg	Tween-80 in ml	PEG-200 in ml	Ethanol in ml	Pluronic- F-68 in mg	Oleic acid in ml
S1	50	5	2.5	2.5	_	5
S2	30	5	2.5	2.5	20	5
S3	50	3.7	3.7	3.6	_	4
S4	30	3.7	3.7	3.6	20	4
S5	50	3	4.5	4.5	_	3
S6	30	3	4.5	4.5	20	3

Table 2: Standard calibration curve of Simvastatin

S. No.	Concentration (µg/ml)	Absorbance at 239 nm
0	0	0.000
1	4	0.171
2	6	0.253
3	8	0.337
4	10	0.421
5	12	0.514
6	14	0.602
7	16	0.694

Table 3: Diffusion Drug release data of formulation S1 to S6

Time (min)	% drug release from the formulation					
	S1	S2	S3	S4	S5	S6
0	00.00	00.00	00.00	00.00	00.00	00.00
10	13.5	15.75	13.5	18	18	13.5
20	20.25	24.75	22.5	27	24.75	22.5
30	31.50	31.5	33.75	33.75	31.50	31.5
40	40.50	40.5	40.5	42.75	42.75	40.75
50	49.5	47.25	51.75	47.25	49.5	51.75
60	60.75	58.5	60.75	60.75	58.5	60.75
90	67.5	67.5	69.75	69.75	67.5	67.5
120	78.75	76.5	78.75	76.50	76.5	78.75
150	83.25	85.5	83.25	83.25	83.25	85.5
180	90	90	92.25	90	92.2	90
210	96.75	94.5	96.75	96.75	94.5	96.75
240	92.25	90	90	92.25	90	90

Table 4: Data showing solubility of Simvastatin

Vehicle	Solubility of simvastatin (mg/ml), mean ± S.D
Ethanol	137.6±4.89
PEG-200	99.5±1.12
Tween-80	70±1.55
Oleic acid	62.5±1.24

Table 5: Data Showing Percentage drug content of the formulations

Formulations	Abs. of drug	Abs.of formulations	% of drug content
S1	0.327	0.324	99.08
S2	0.327	0.297	90.82
S3	0.327	0.312	95.41
S4	0.327	0.298	91.13
S5	0.327	0.318	97.24
S6	0.327	0.291	88.99

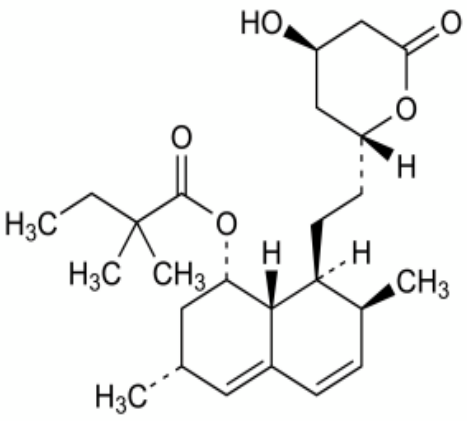

Fig. 1: Structure of simvastatin

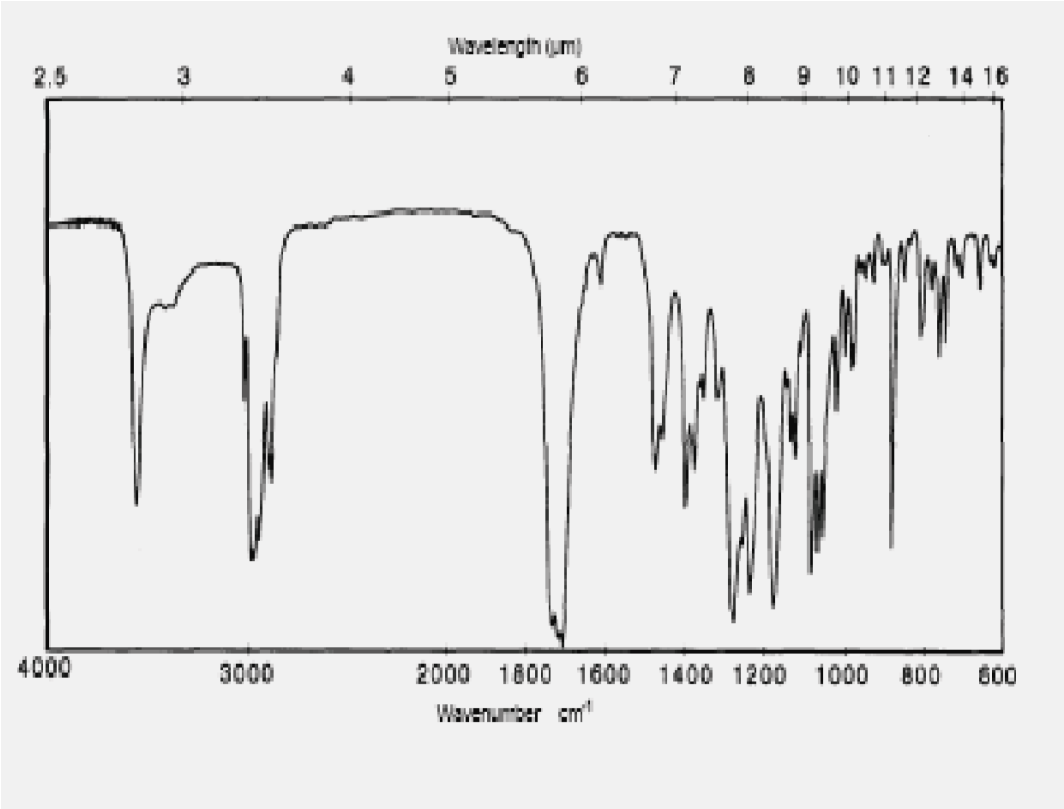

Fig. 2: IR spectra of Simvastatin

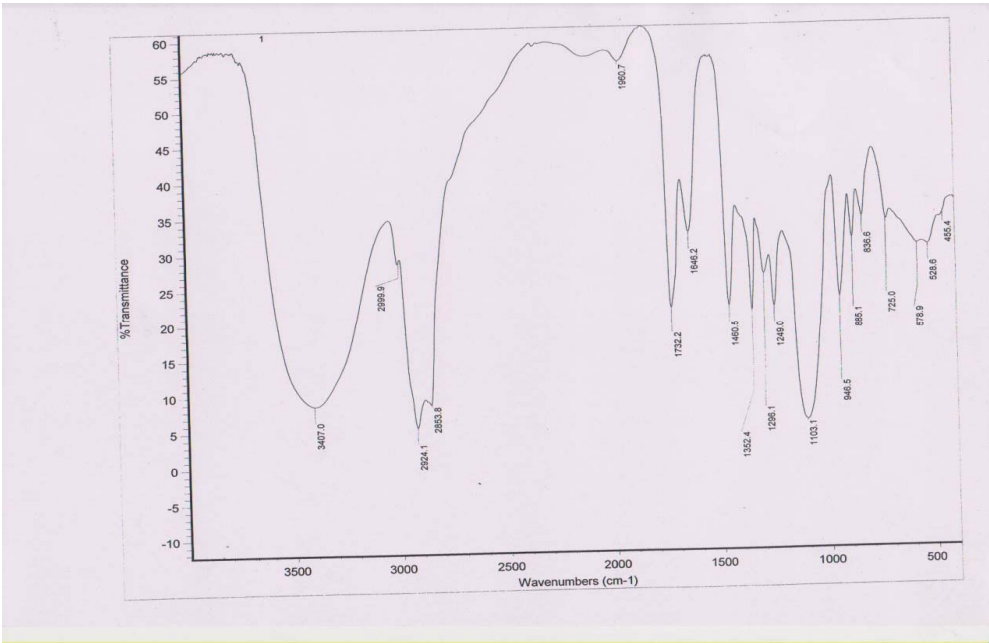

Fig. 3: IR spectra of Formulation S1

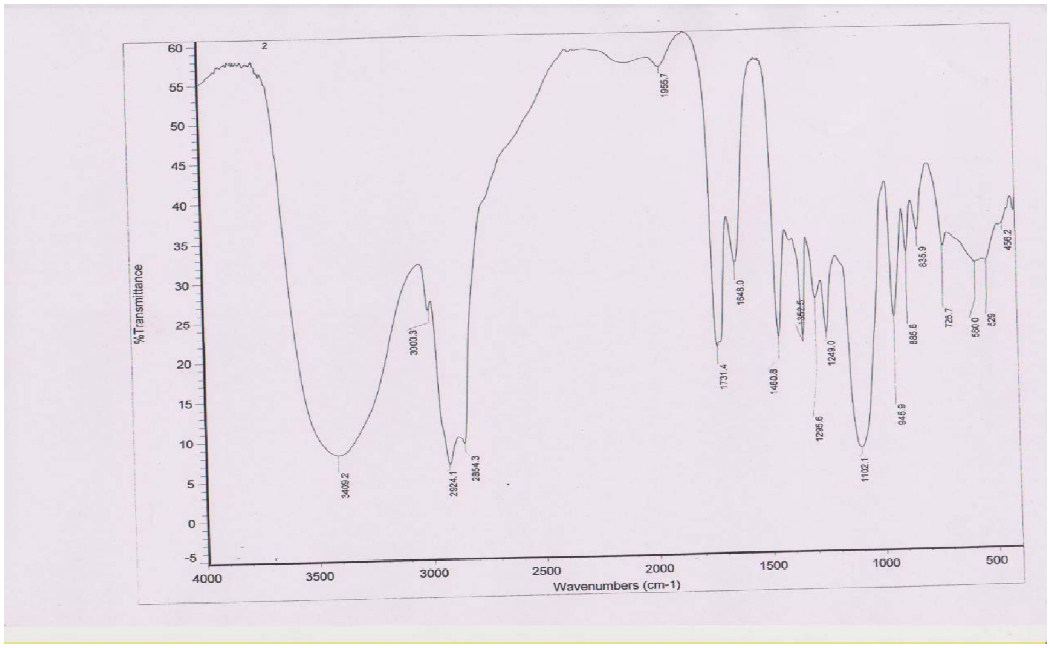

Fig. 4: IR spectra of Formulation S2

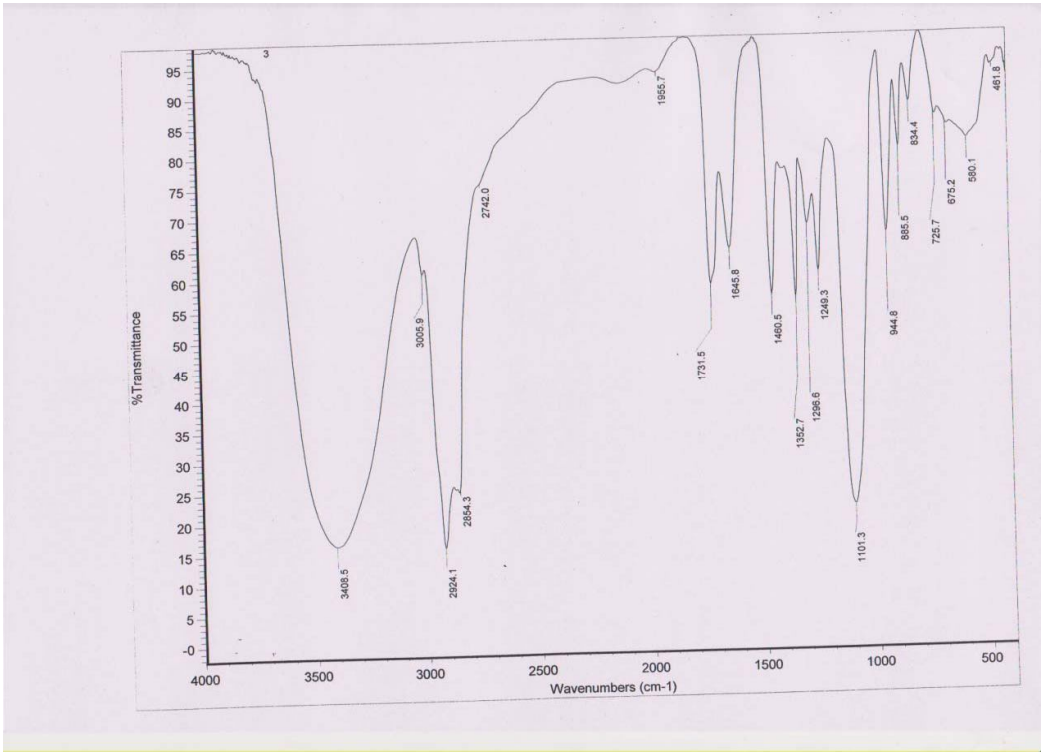

Fig. 5: IR spectra of Formulation S3

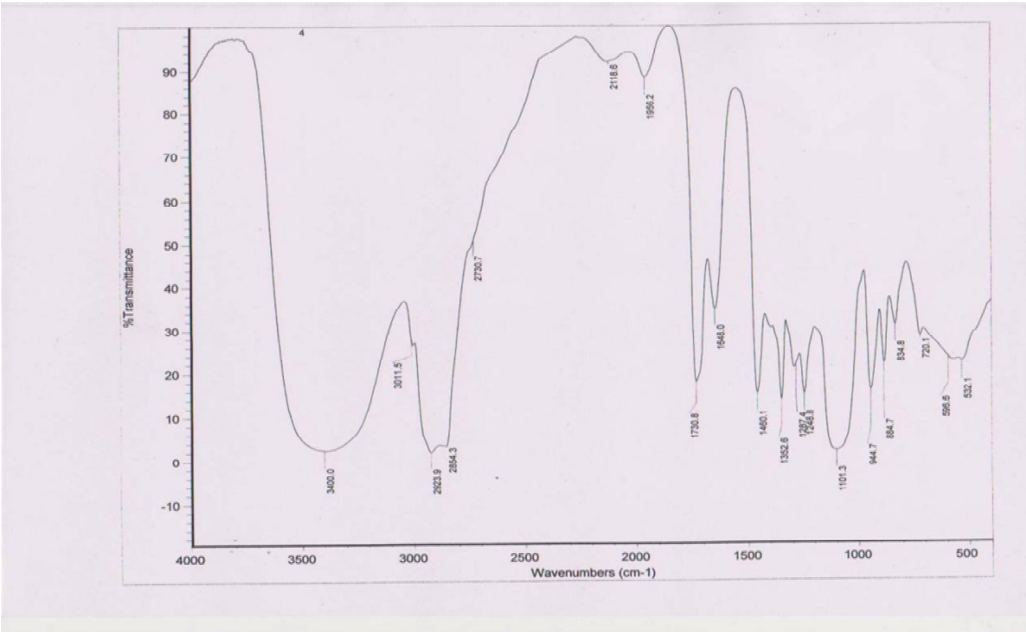

Fig. 6: IR spectra of Formulation S4

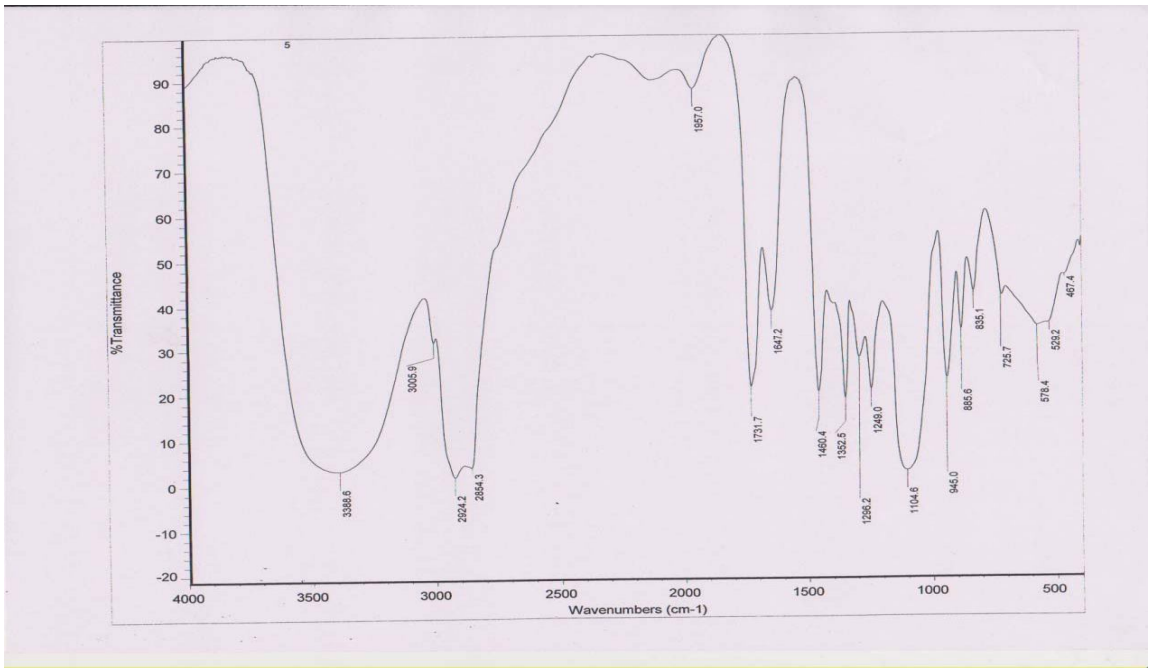

Fig. 7: IR spectra of Formulation S5

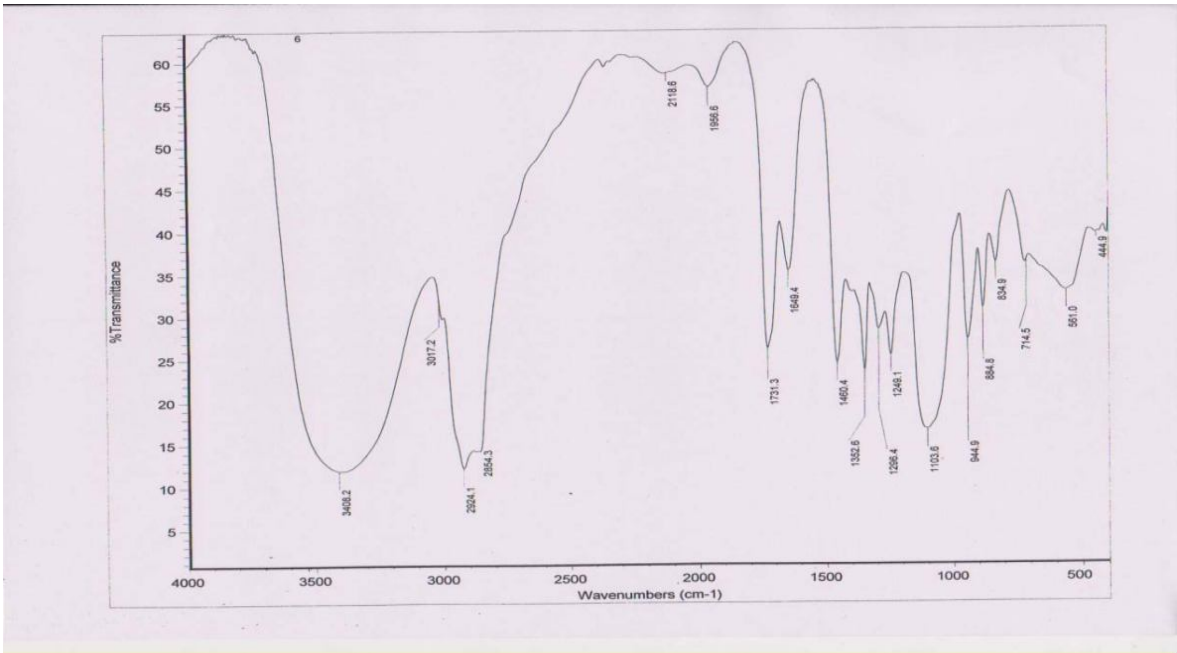

Fig. 8: IR spectra of Formulation S6

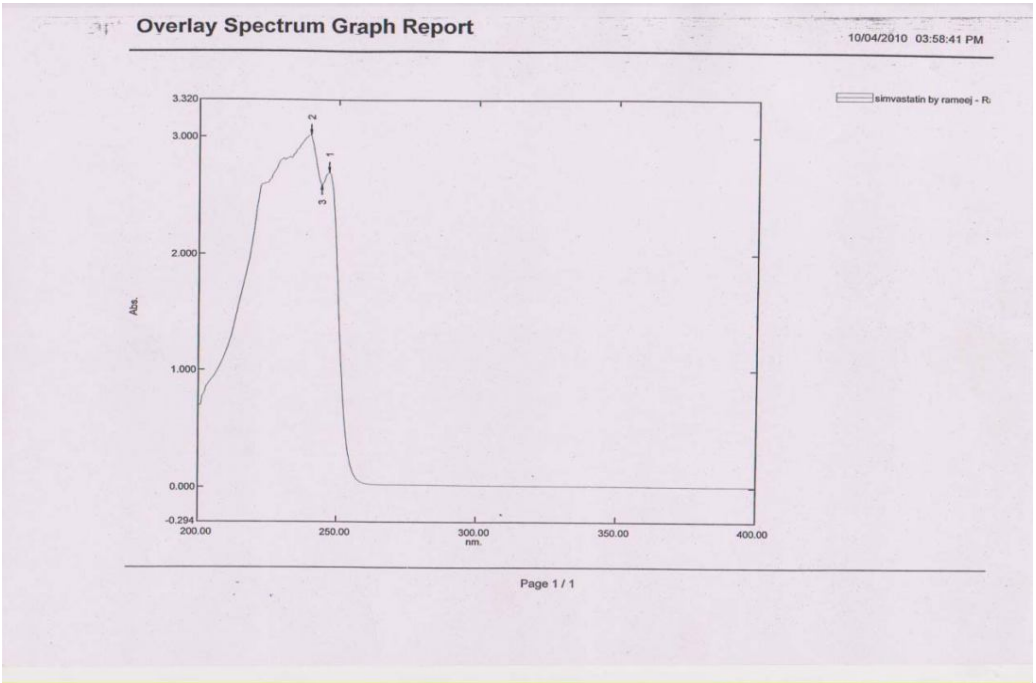

Fig. 9: Absorbance of Simvastatin

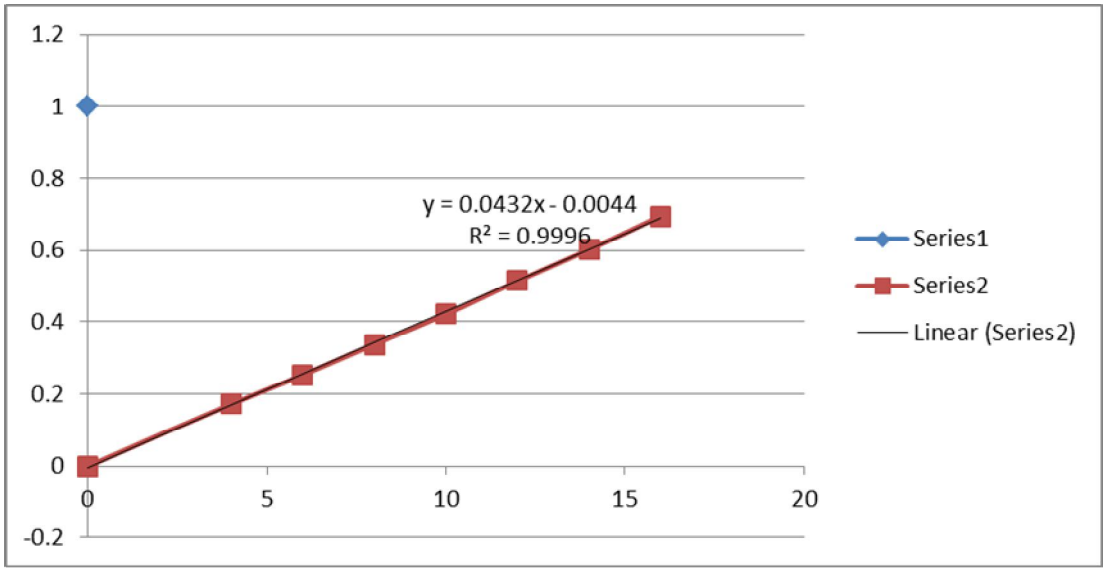

Fig. 10: Calibration Curve of Simvastatin

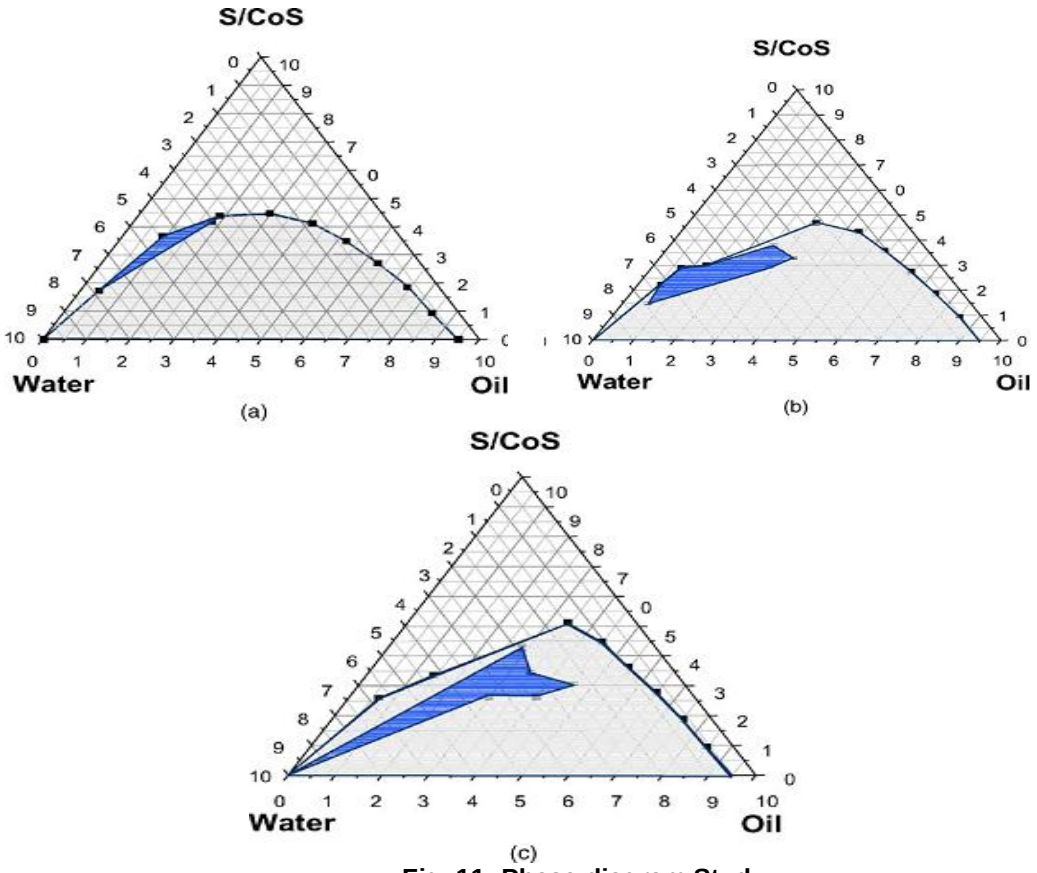

Fig. 11: Phase diagram Study

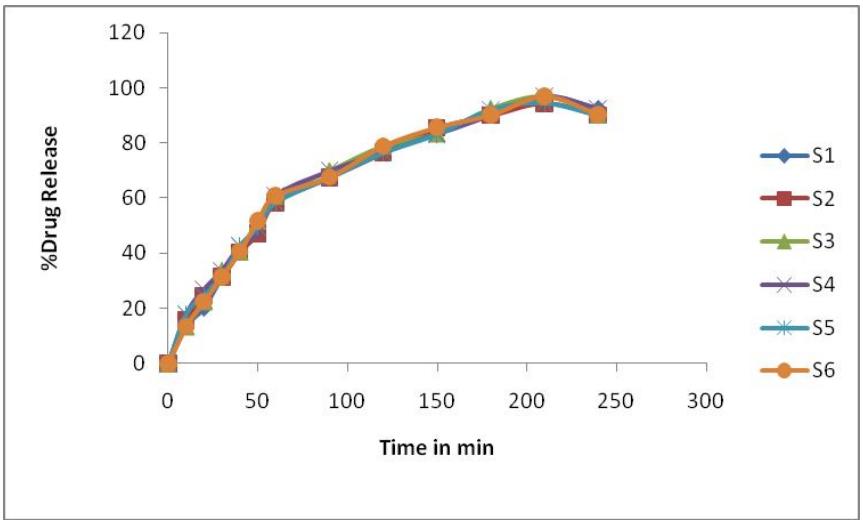

Fig. 12: Drug Release Profile of S1-S6

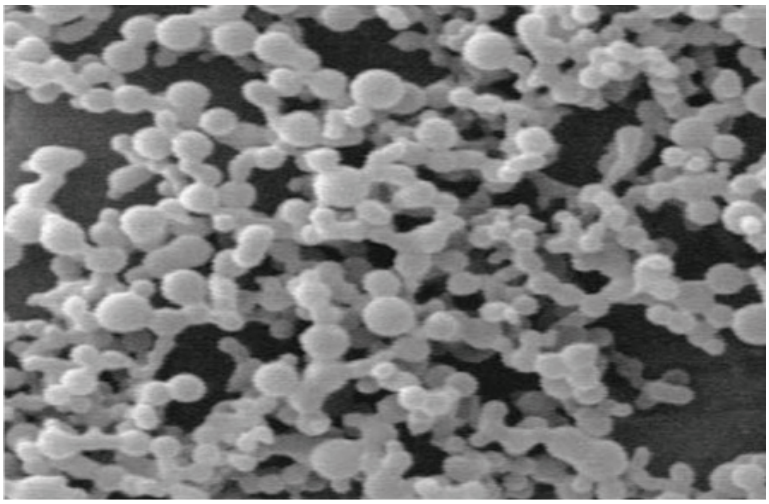

Fig. 13: SEM of Formulation S1

CONCLUSION

Self emulsifying drug delivery systems are a promising approach for the formulation of Simvastatin. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability with future development of this technology. SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

Results of this study indicated that in vitro drug release varied with the release media. From the drug content study it is found that all the formulation contain above 90% of drug. Formulation S1 and S4 was given maximum up to 92.25 % drug release from the formulation. From the SEM study the average particle size was found to be within 50 nm and the shape was found to be spherical.

From the above said it can safely conclude that the Self Emulsifying Drug Delivery System of simvastatin showed a better bioavailability. Further it is advised that the same work should be confirmed for its therapeutic efficacy with the experimental

and clinical trials.

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