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Formulation and Optimization of Pravastatin Loaded Self Emulsifying Drug Delivery System

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ABSTRACT
In this study, we have prepared Paravastatin SNEDDS in liquid and solid form, in order to improve the solubility of poorly water soluble drugs. Liquid SNEDDS contain lebrasol (oil phase), Cremophor RH 40 (surfactant) & Transcutol HP (co-surfactant) were thermodynamically stable and produced clear nanoemulsions upon dilution. After that the liquid formulation were transformed in solid SNEDDS from adsorption into the syloid 3150, Neusilin US2 and aerosol. The absorbent-based solid SNEDDS maintained the self-nano-emulsification properties of the original liquid SNEDDS formulations, with solid state analysis suggesting that the drug had remained in a dissolved state within these formulations.
Retentive, physical characterization of the carrier-based solid SNEDDS formulations showing that drug was molecularly dispersed within the system and that the self nano-emulsifying properties of the carrier were unchanged. The only exception was those formulations prepared at the highest drug: carrier ratio (3: 10). For both absorbent-based and carrier-based solid SNEDDS, the in vitro dissolute on efficiency was significantly higher than that obtained for the pure drug. However, incorporation of adsorbents into Gelucire -based solid SNEDDS formulations resulted in reduced dissolution of the drug. Gelucire 48/16-based solid SNEDDS prepared at 50^{o}C were more physically stable to storage at 30^{o}C 75% RH for 6 months than formulations processed at 40oC, suggesting that complete melting of the carrier during manufacture is essential for production of physically stable formulations. In general, a range of liquid, solid and carrier-based SNEDDS formulations effectively evolved and offer useful alternatives to improving the solubility of poorly water-soluble drugs.

I. MATERIALS AND METHODS

Table.1 List of Chemicals

S. No.	Chemicals	Brand
1	Pravastatin	A gift sample form sigma Aldrich
2	Labrasol (oil)	Shreedhar Enterprise Delhi
3	Cremophor RH 40 (surf)	Sigma- Aldrich
4	Transcutol HP	-
	polyethylene glycol	Acuro Organic Limited New Delhi
	Tween-20(Surfactant)	Translam Institute
5	Laurogycol	-
6	Avicel	-
	Neusilin US2	Samridhi Crreation Gurhaon

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Instrumentation:

Table.2 Lists of Instruments Used

S. No	Instrument	Manufacture
1.	U.V Spectrophotometer	Lab india 3000
2	FTIR spectrophotometer	Shimadzu8300
3	SEM & TEM	-
4	Dissolution Apparatus	
5	Magnetic stirrer	Remimotors, Ahmadabad.
6	Mechanical stirrer	Remimotors, Ahmadabad
7	Electronic balance	Sartorius
8	Digital pH meter	Digisun,Hyderabad
9	Digital melting point apparatus	CL725/726, Microcontroller based melting point apparatus

Methods:

Selection of Oil:

The solubility of Pravastatin in each of the oils determined by mixing little excess of drug with the vehicles in sealed glass containers followed by vertexing for 5min. The contents are later subjected to steady mixing over shaker bath for 72hrs at 37°C at 300rpm followed by centrifugation at 10,000rpm for 10–12min. Contents filtered and concentration of drug determined spectrophotometrically at 304nm. The study executed in triplicate and mean value recorded [84].

Selection of Surfactant:

0.03g of various surfactants mixed with selected oil phase, vortexed for 60s and 0.01g of the mixture diluted with distilled water to obtain emulsion. The % transmittance (%T) of all samples analyzed at 304nm. The study executed in triplicates and means values recorded [85]

Selection of Co-surfactant:

A mixture of 300ml of oil, 200ml of optimized surfactant, and 100 ml of chosen co-surfactants were vortexed. Weighed amount of this mixture is diluted to form emulsion and evaluated for % transmittance at 304 nm .The study executed in triplicate and mean value recorded [86].

Construction of Pseudo-ternary Phase Diagram:

From pseudo-ternary phase diagram the self-emulsify region under dilution and agitation can be identified by visual test method. Surfactant and co-surfactant (Smix) mixed in diverse ratio (1:1, 1:2, 1:3, 2:1, 3:1, and 4:1). Further for each S mix, oil and specific S mix of about 17 ratios ranging from 1:9 to 9:1. From the mixtures, 0.1ml was taken in the beaker to which 100 ml water added, contents mixed using magnetic stirrer. The % transmittance of the formed emulsion was checked at 304 nm using UV visible spectrophotometer. The resultant emulsion was checked for clarity, phase separation and coalescence of oil droplets. Emulsions showing phase separation and coalescence were judged as unstable emulsions. Ternary phase plots drown by recognizing good self-emulsifying region with oil, S mix, and water where each of them representing apices of triangle [87].

Preparation of Pravastatin loaded SNEDDS:

Based on solubility study the oil phase (Labrasol), surfactant (Cremophor RH40), and cosurfactant (Transcutol HP) were chosen for formulation of Pravastatin SNEDDS. 40mg of drug added to oil at 40°C for complete dissolution followed by addition of surfactant and co-surfactant and soni-cated for 60 min. Seventeen such formulations prepared and filled into size 0 gelatin capsule shells [88].

Physicochemical evaluation of Pravastatin SNEDDS:

Developed Pravastatin SNEDDSs were physicochemical evaluated for droplet size (DS), Zeta potential (ZP), entrapment efficiency, drug content and cumulative % drug release.

DS and Zeta Potential:

The DS and ZP of all 6 formulations determined by Zetasizer Nano ZS90 dynamic light scattering particle size analyzer (Malvern, Worcestershire, UK) as per the method referred [89].

Entrapment Efficiency:

A known quantity of SNEDDS mixed with 100ml phosphate buffer (pH 7.4) and kept in dark for 24 h. The contents filtered, filtrate diluted, and analyzed for drug content at 304nm [90].

Percentage Drug Content:

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All the 6 formulations of Pravastatin SNEDDS were analyzed for assay by dissolving accurately weighed samples in 10ml carbinol and vortexed mixer for 10min. Each of the samples filtered, and drug content of filtrate analyzed spectrophotometrically against blank at 304nm [91].

Cumulative Percentage Drug Release:

studies of Pravastatin SNEDDS Drug release tests on each batch of the SNEDDS carried out using a USP I dissolution rate test apparatus at 50rpm and temperature of 37±0.5°C. An amount of the SNEDDS equal to 40mg of drug filled into hard gelatin capsule (size no.0), placed in the dissolution medium containing 900ml of phosphate buffer (pH 7.4). The analysis carried out as preferred method and samples analyzed using RP- HPLC UV detector at 304nm [92].

Characterization of Pravastatin SNEDDS:

Fourier transform infrared (FTIR) spectroscopy FTIR spectrophotometer (Shimadzu FTIR 8400S, Japan) was used to record the FTIR spectra of pure drug and drug loaded SNEDDS in 4000–400cm-1 range [93].

Surface Morphology:

Scanning electron microscopy studies (JEOL JEM 2100 F, USA) were carried out by diluting the same with distilled water to 1000 times and then plunging on a 2% uranyl acetate solution stained carbon grid [94].

Stability Studies:

Stability testing was conducted as per the ICH guidelines for 3 months in stability chamber. The samples were withdrawn at predetermined intervals 0, 30, 60, 90 and 180 day's period. Various in vitro parameters such as drug content, entrapment efficiency, and in vitro release studies were evaluated [95].

II. RESULTS AND DISCUSSION

Standard calibration curve of Pravastatin in Methanol:

The standard calibration curve of Pravastatin was constructed in methanol to obtain different concentrations ranging from 2.5 to 45µg/ml, for which the absorbance readings were determined spectrophotometrically at λ_{max} 304nm. The standard calibration curve was linear over the concentration range studied and obeys Beer-Lambert's law with a correlation coefficient (r^2) 0.999. The corresponding regression equation was found to be Y = 0.0179X – 0.0043.

Table.3 standard calibration curve of Pravastatin in methanol assayed spectrophotometrically at λ_{max} 304nm

S.NO	**Conc.**	Abs. **±SD (n = 3**
1	2	0.049 ± 0.002
2	5	0.087 ± 0.001
3	10	0.169 ± 0.001
4	20	0.261 ± 0.003
5	25	0.329 ± 0.002
6	30	0.424 ± 0.002
7	35	0.510 ± 0.005
8	40	0.601 ± 0.004
9	45	0.702 ± 0.003
10	50	0.726 ± 0.002

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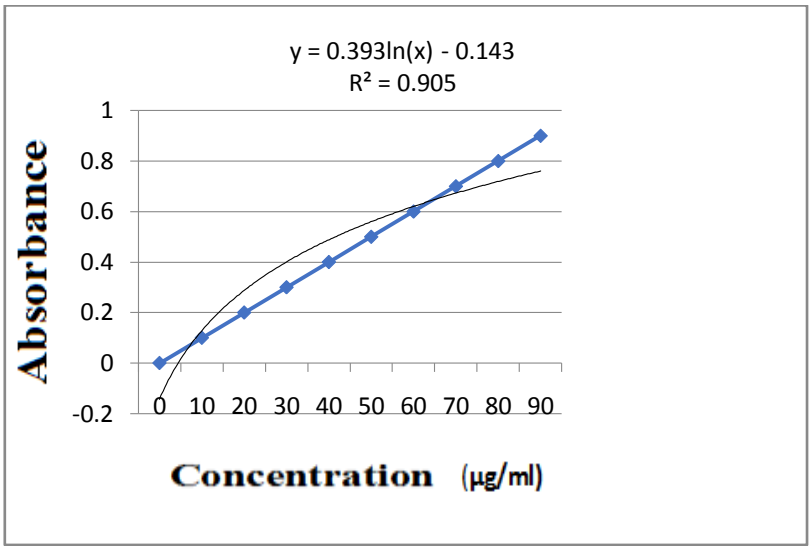

Fig.1 Standard calibration curve of Pravastatin

Solubility Analysis of Drug in Different Solvent:

Results of the solubility testing of Pravastatin in different oils, surfactants, co-surfactants and water are shown in b e l o w Fig. It is apparent that Pravastatin wasmore soluble in various vehicles used compared to its resulting solubility in water.

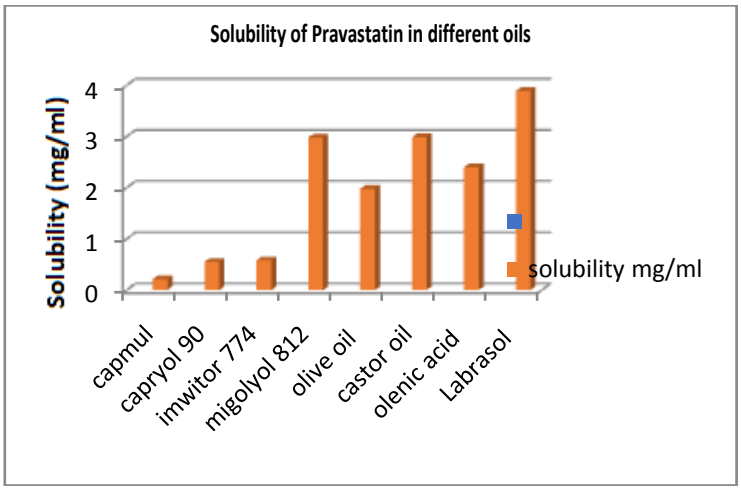

Fig.2 Solubility of Pravastatin in different oils

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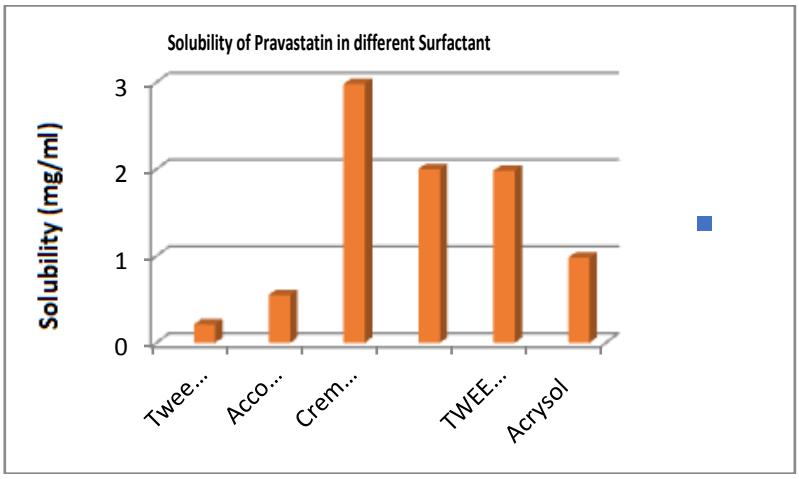

Fig.3 Solubility of Pravastatin in different Surfactant

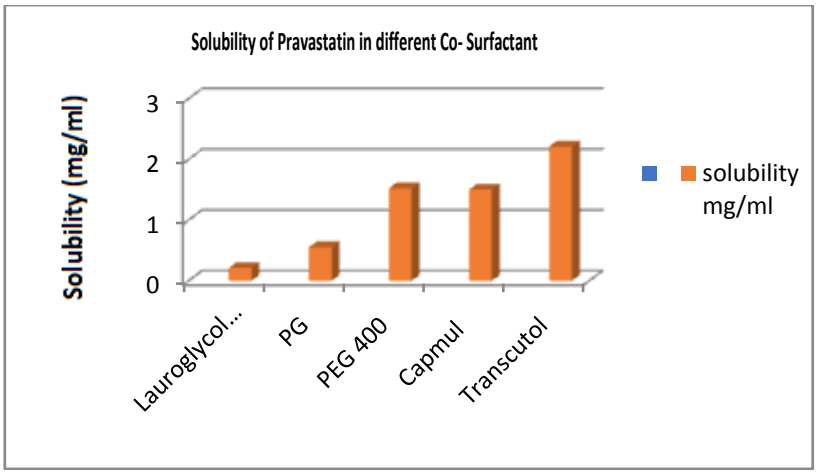

Fig.4 Solubility of Pravastatin in different Co- Surfactant

Formulation chart of S mix with Drug:

Table.4 Formulation chart Pravastatin Loaded Self Emulsifying

F CODE	Pravastatin (Mg)	Capryol 90	Tween 20 (mg)	Tween 80 (mg)	Transcutol (mg)	Cremophor RH (mg)
F1	40	45	48	35.6	52	**x**
F2	40	35	72	45.1	48	**x**
F3	40	52	**X**	**x**	15.9	34.1
F4	40	28	**X**	**x**	13.2	38.1
F5	40	52	**X**	**x**	24.1	45.9
F6	40	28	**X**	**x**	16.8	51.8

Determination of Solubility in Different Selected Formulation:

Table.5 Solubility in Different Selected Formulation

F. code	SATURATED SOLUBILITY (MG/G)
F1	41.64 ± 1.56
F2	37.53 ± 1.42
F3	39.93 ± 0.89

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F4	34.88 ± 0.83
F5	44.45 ± 1.21
F6	33.20 ± 0.59

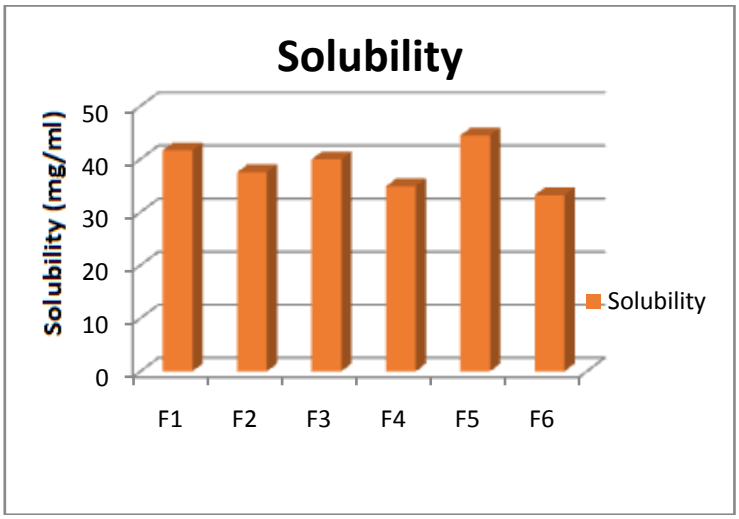

Fig.5 A Graphical Presentation of Solubility in Different Selected Formulation

Characterization of Pravastatin -loaded SNEDDS:

Table.6 Characterization of Pravastatin -loaded SNEDDS

F Code	Mean Deoplet Size (nm) ± SD	Mean PDI ± SD	Mean Zeta potential (mV)	Zeta deviation (MV)
F1	198.90 ± 9.59	0.350 ± 0.037	-29.4	4.8
F2	299.60 ± 0.14	0.290± 0.001	-36.0	4.9
F3	40.25 ± 0.79	0.236 ± 0.001	-21.8	-21.9
F4	44.58± 1.21	0.245± 0.001	-30.9	-30.4
F5	19.24± 0.84	0.108± 0.020	-24.4	-24.1
F6	21.78± 0.59	0.129± 0.004	-15.1	-15.2

FTIR Study:

Fourier transform infrared (FTIR) spectroscopy FTIR spectrophotometer (Shimadzu FTIR 8400S, Japan) was used to record the FTIR spectra of pure drug and drug loaded SNEDDS in 4000–400cm-1 range.

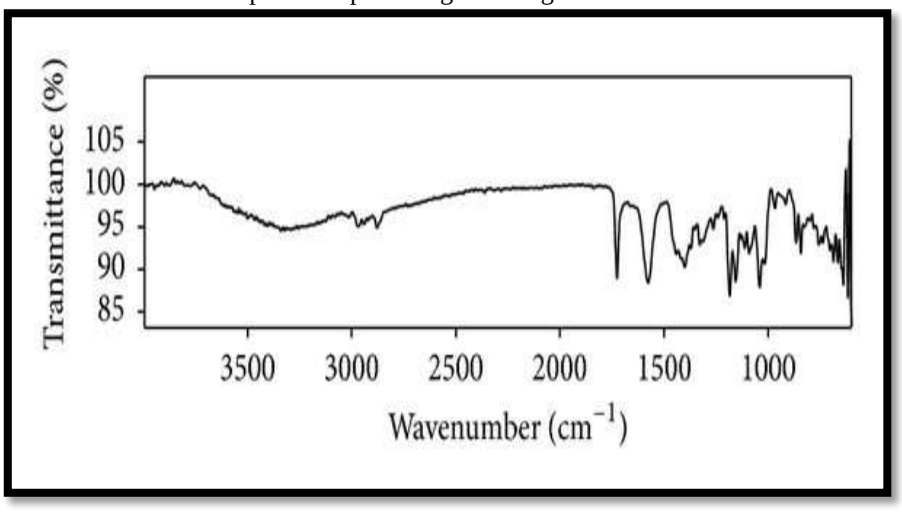

Fig.6 FTIR of Pure Drug

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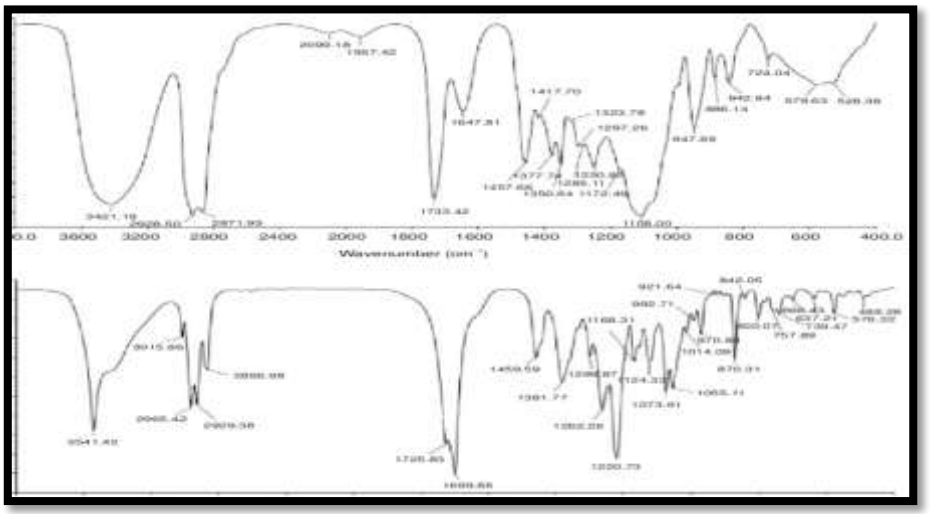

Fig.7 FTIR of drug and Oil (Labrasol)

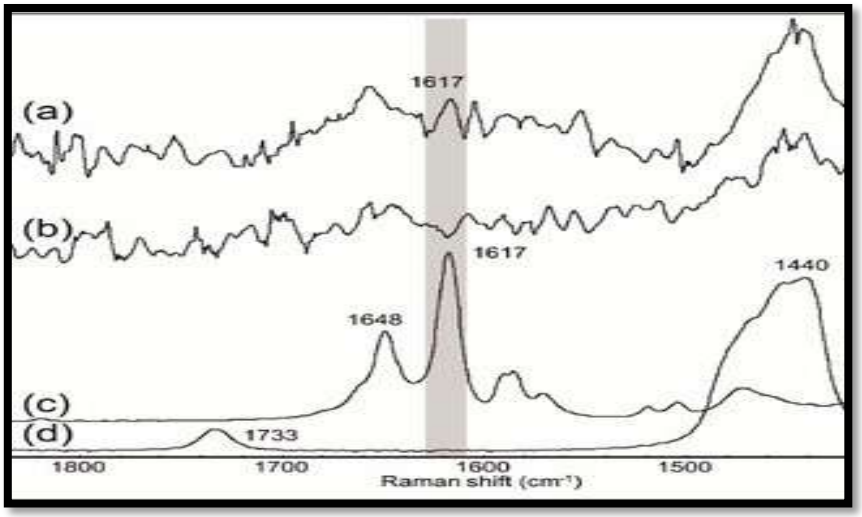

Fig.8 FTIR of Drug with surfactant (Cremophor)

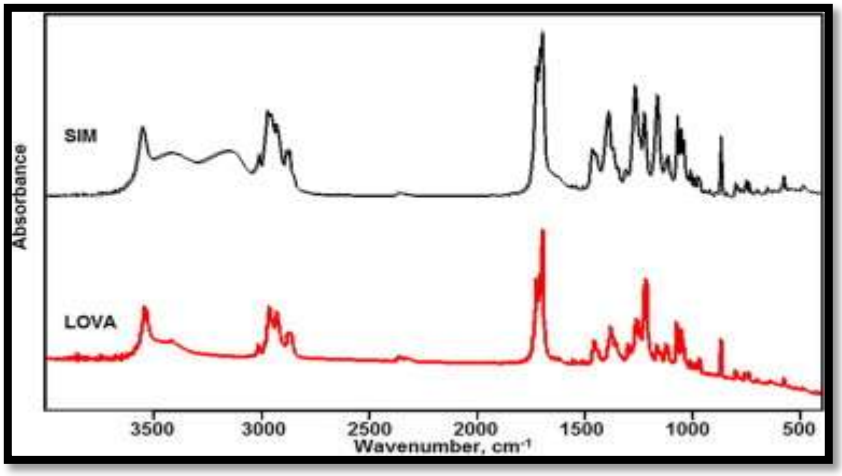

Fig.9 FTIR of Drug with Co-surfactant (Transcutol)

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SEM Analysis:

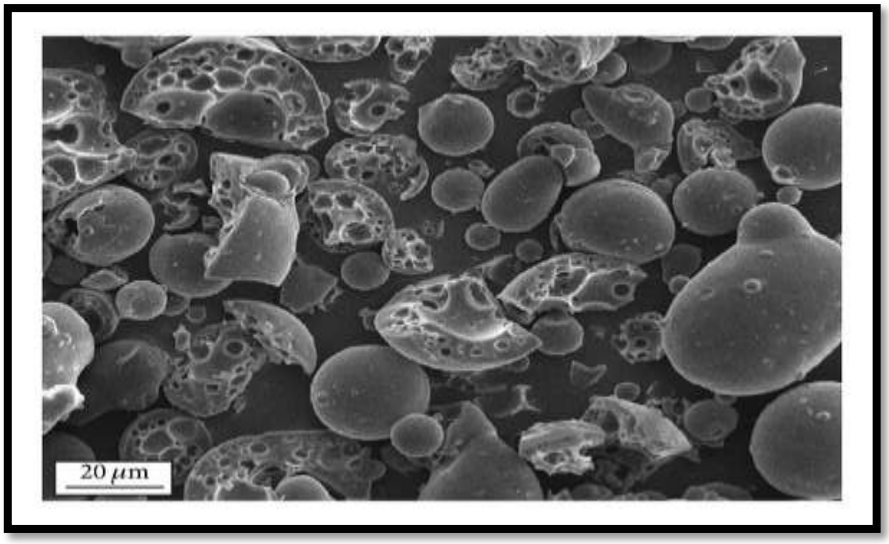

Fig.10 SEM analysis of Paravastatin

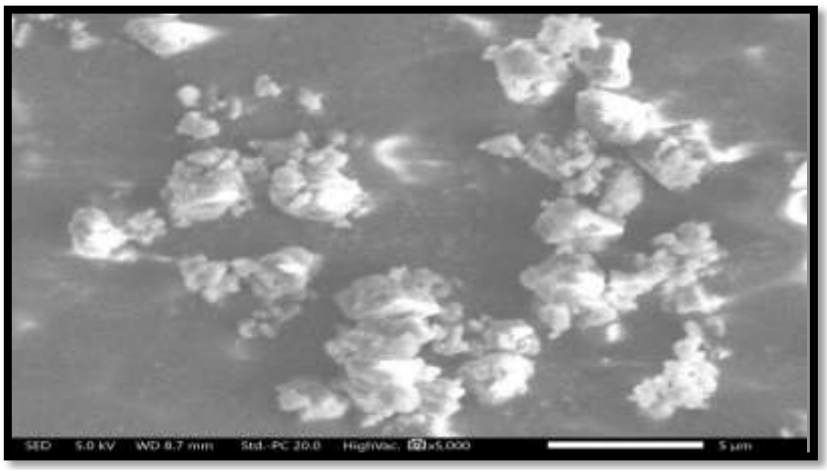

Fig.11 SEM analysis of Cremophor

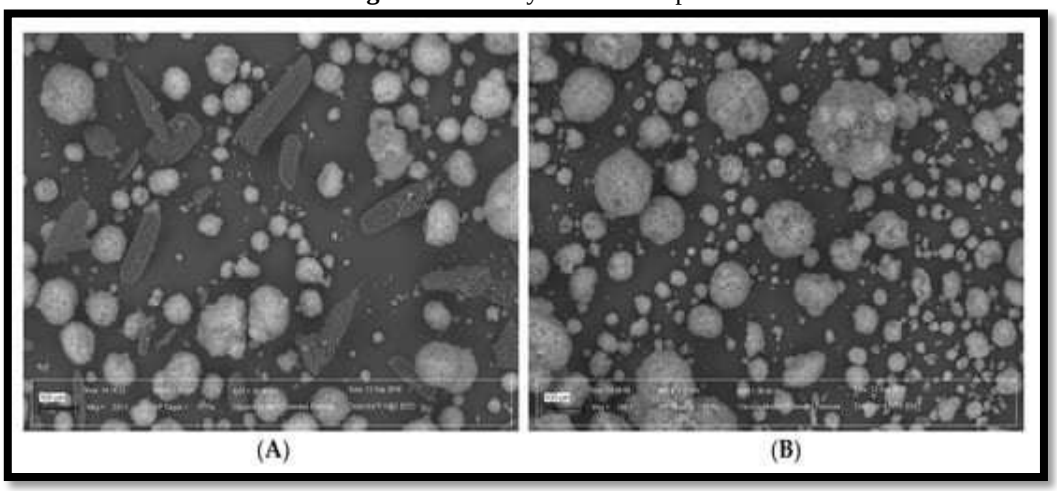

Fig.12 SEM analysis of Transcutol HP and Labrasol

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% Drug content and Entrapment efficacy:

Table.7 % Drug content and Entrapment efficacy

F Code	% Drug content	% Entrapment efficiency
1	97.52±0.15	95.11±0.073
2	98.25±0.15	94.78±0.073
3	97.85±0.15	95.14±0.073
4	96.25±0.15	96.12±0.073
5	99.05±0.15	96.98±0.073
6	97.02±0.15	95.89±0.073

Percentage Drug Release:

Table.8 % Drug Release

Time (Min)/F. CODE	F1	F2	F3	F4	F5	F6
5	31.25±1.11	30.75±1.12	39.43±1.45	32.35±1.10	39.43±1.45	39.43±1.15
10	38.58±1.85	40.45±1.95	41.52±1.01	40.58±2.9	55.66±1.04	48.66±1.25
15	39.98±2.25	45.49±2.42	49.25±2.21	52.28±2.10	66.76±2.41	56.76±2.14
20	45.20±2.11	55.35±2.12	56.45±2.71	66.76±2.8	79.84±2.78	71.84±2.02
25	51.12±2.12	67.39±2.52	69.25±2.52	74.62±1.99	88.66±2.84	82.66±2.14
30	68.52±2.71	79.13±2.78	82.25±1.7	84.44±2.45	96.25±1.14	90.51±1.45

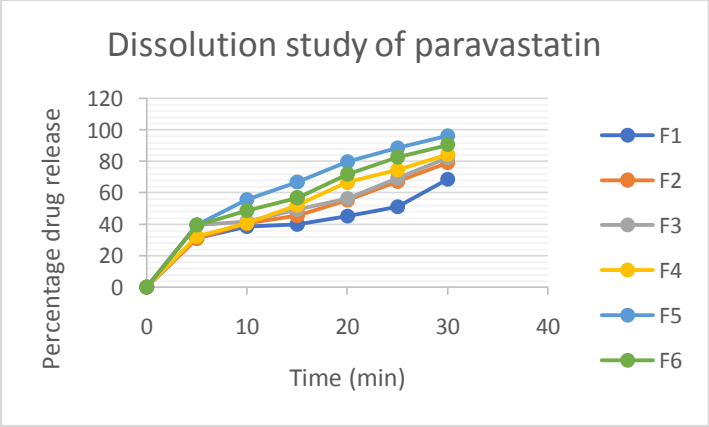

Fig.14 Dissolution Study of Optimized Formulation from different drug-loaded solid SNEDDS

III. DISCUSSION:

Dissolution of Paravastatin from different drug-loaded SNEDDS prepared with different solid carriers was carried out in phosphate buffer pH 7.2 and compared to the dissolution from pure drug. The dissolution profiles obtained are shown in above fig. It was observed that hard gelatin capsules disintegrated and released its content after 90 seconds of the start of the dissolution studies. Different solid SNEDDS showed maximum percentage of drug release within 15-30minutes, however, the dissolution studies were continued for 1 hour to detect any precipitation or variation that may occur over a period of time. However, comparison of different dissolution profiles based

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on this approach of single point measurement may not sufficiently characterize the dissolution process.
So The maximum drug release found within the formulation F5 that containing the best ration of surfactant and Co- surfactant give the maximum drug release it has been found 96.25±1.14% within 30min.

Stability Studies:

Table.9 Stability Study for Best Formulation F5

S. No.	Parameters	Initial	1 Month	3Month	6Month
1	Entrapment efficiency	96.98±0.073	97.12±0.071	97.00±0.014	69.87±0.025
3	drug content	99.05±0.15	99.01±0.15	98.45±0.15	98.12±0.15
4	In-Vitro Drug Release	96.25±1.14	96.21±0.12	95.85±0.0.21	95.24±1.08

IV. CONCLUSION

In this part of the study, formulation of solid SNEDDS formulations from liquid SNEDDS was investigated in order to avoid different disadvantages associated with conventional filling of liquid formulations into capsules. Drug-loaded solid SNEDDS were developed by adsorption of liquid SNEDDS formulations onto solid carriers. Enhanced dissolution behavior was dependent on the physicochemical properties of carriers used in formulations and this variation was supported by dissolution parameters calculated for different formulations. Slyod showed optimum dissolution behavior compared to other solid SNEDDS formulations tested. This was due to low specific surface area of the carrier which enhanced dispersion of the drug in the dissolution medium and led to rapid formation of spontaneous nano-emulsion with small droplet size. Therefore, properties of solid carriers have great impact on drug dissolution profile from solid SNEDDS and thus must be considered in rationalizing development of solid SNEDDS formulations. Increased dissolution of Pravastatin from solid SNEDDS formulations suggests that kind formulations may represent promising systems for oral administration of poorly soluble (BCS class II) drugs such as Pravastatin.