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DEVELOPMENT AND EVALUATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM FOR TELMISARTAN

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Keywords:

Telmisartan, Self nano-emulsifying Drug delivery system, Lipophillic, Ternary phase diagram, Bioavailability

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ABSTRACT: Self nano-emulsifying system drug delivery system (SNEDDS) is promising for drugs of BCS class II. The objective of present study to develop self nano-emulsifying drug delivery system for Lipophillic drug Telmisartan (antihypertensive drug), labrafil 1944, Kolliphor ELP: Span 80 (1:1) and PEG 400: Ethanol (1:1) was chosen as oil, Surfactant and Co-surfactant as they show higher solubility for Telmisartan. Screening of Surfactant, Co-surfactant done by percent transmittance and were also observed for turbidity or phase separation visually. Pseudo ternary phase diagram were constructed to identify the self emulsifying regions and also to establish the optimum concentration of oil, surfactant and co-surfactant. Box bhenken desine applied for optimization of formulation. Prepared formulation further Characterization done. Percent Drug Content found 99.71, thermodynamic stability studies show homogenous and no phase separation, Emulsifying Study performed transparent appearance after 24 hr, for robustness Dilutability in water and 0.1N HCl give Percentage Transmittance 99.5 and 100, conducting *in vitro* dissolution test compared with marketed preparation in stimulated gastric (S.G.F) pH 1.2 showed Percent Drug Release 93.98 with in 30 min, compared by pure drug which was 14.26. Particle size found 164.9 nm which is under nano size range, performing Poly Dispersity Index (PDI) 0.228, Zeta Potential found to be -26.0 mV, by using particle size analyzer.TEM study shows uniform spherical nano emulsion droplets. From the present study it is clear that SNEDDS can be formulated to improve the dissolution and oral bioavailability of poorly water soluble drug Telmisartan.

INTRODUCTION: Telmisartan is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Telmisartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so blood can flow more easily [1]. Biopharmaceutics Classification System (BCS) classification II, that is, highly permeable and low soluble [2].

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Oral route is preferred route of drug administration as facilitates more convenient to drug uptake. It has been estimated that 40 - 70% new chemical entities (NCE) having poor aqueous solubility shows low bioavailability problem is a major hurdle as well as drugs not have dose linearity is a matter to be concerned. Research now a day focus on improving dosage forms design by controlling release rate, enhancing drug solubility or dissolution rate enhancing drug permeability across bio-membrane, enhancing drug stability.

Oral bioavailability of the drugs through gastrointestinal tract depends on the lipophillicity and solubility profile of the drugs. Factor responsible for determination of oral bioavailability

are drug stability in gastro intestinal tract, intestinal permeability, resistance to metabolism by cytochrome P450 enzymes present in gut enterocytes and liver hepatocytes and interaction with efflux transport system like p-glycoprotein (p-gp) physiological pathway.

An ideal oral drug delivery system must protect the drug from degradation in the gastrointestinal tract, and deliver the bioactive compounds to the specific area where it is better absorbed [3].

SNEDDS are transparent, thermodynamically stable isotropic concoction of lipid, surfactant, co-surfactant and drug substances that rapidly form oil - in water nanoemulsion when introduced into aqueous media under gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification *in vivo* [4 - 6]. The self-emulsification process occurs spontaneously because the free energy required to form the micro nanoemulsion is either low and positive, or negative [7]. SNEDDS with globule size ranging between 20 - 200nm are called self micro emulsifying drug delivery system (SMEDDS) [8].

MATERIAL AND METHODS:

Materials: Telmisartan was generous gift sample from torrent research center, Bhat, Gandhinagar, Gujrat, India. Labrafil 1944, Transcutol recived as gift sample from gettefosse, Mumbai, Maharashtra India, kolliphour ELP, kolliphour RH40 were received as gift sample from BASF Mumbai, Maharashtra. PEG 400, Span 80, ethanol were brought from Merck India, Mumbai and S. D. fine chem India.

Determination Telmisartan Solubility Study in Various Oils: The solubility of Telmisartan in various solvents was determined by dissolving excess amount of Telmisartan in 1ml of each of the selected solvents in 5ml capacity Stoppard vials separately. Each glass vial was then mixed for 10 min using a vortex mixer. The mixture vials were then kept at 37 ± 1.0 °C in a shaker bath for 72 h to get equilibrium. The equilibrated samples were removed from shaker and centrifuged at 18000 rpm for 30 min. The supernatant was taken and filtered through a 0.45µm membrane filter. The concentration of API was determined in each solvent by UV spectrophotometer by scanning from 200 - 400nm [9]. The use of long chain triglycerides (LCT) leads to increased lymphatic transport is used to enhance oral drug bioavailability [10].

Screening of Surfactants: For this study, 150mg of surfactant were added to 150mg of oily phase and then this mixture was heated at 50 °C for homogenization of the components. Then from each prepared mixture, 100mg was withdrawn and diluted to 100ml in a volumetric flask. The ease of emulsification was judged by the number of flask inversions required to yield homogeneous emulsion. The emulsions were allowed to stand for 24 hrs and then % transmittance was evaluated by using UV spectrophotometer [11, 12]. They were also observed for turbidity or phase separation visually the surfactant chosen must be able to lower the interfacial tension during the formation of nanoemulsion. Surfactants are amphillic in nature and generally dissolve or solubilize relatively high amount of hydrophobic drug compounds [13]. The key step for SNEDDS formulation is to find a suitable oil surfactant mixture that can dissolve the drug within the therapeutic concentration [14 - 16].

Screening of Co-Surfactants: For screening of selected co-surfactants, the oil: surfactant: co-surfactant was taken as 300mg: 200mg: 100mg *i.e.* in the ratios of 3:2:1. Out of the total 600mg of the mixture 100mg was withdrawn and then added drop wise in a 100ml volumetric flask containing distilled water drop wise; then it was inverted 50-60 times and kept overnight. After which the % transmittance was determined by scanning in the range from 800 - 200nm (wavelength 650nm) using UV - visible spectrophotometer. After the completion of screening the next step was to optimize the combination showing good % transmittance [17].

Ternary Phase Diagram were constructed to identify the self emulsifying regions and also to establish the optimum concentration of oil, surfactant and co-surfactant. Greater the size of nano-emulsion region in phase diagram greater is the self emulsification efficiency.

Phase diagram were constructed using chemix school v.3.51 software and the area of nanoemulsion shaded.

The clarity of the formed aqueous dispersion was visually assessed using the following grading to identify the tested system.

a. Denoting the formation of a clear microemulsion.
b. Denoting the formation of a translucent microemulsion.
c. Represent the formation of a slightly less clear emulsion which had a bluish white appearance.
d. Denoting the formation of a bright white emulsion (similar to the appearance of milk).
e. Denoting the formation which exhibited either poor emulsification with large oil droplets on the surface or the emulsion was not formed.

Type a and b system are most likely expected to have particle size less than 50nm and referred as a self nano emulsifying drug delivery system (SNEDDS). Phase diagrams involve the plotting the three components surfactant: co-surfactant (S_{mix}), oil and water each of them representing an apex of triangle. Ternary mixtures with varying compositions of the components were formed. For any ternary mixture formed the total of surfactants, co-surfactants and oil concentrations always added to 100%. The required amounts of the three components were weighed accurately. The mixture was then gently heated at 45 - 50 °C and vortex to form homogenous mixture. To this mixture distilled water was added drop by drop until a transparent solution was formed. The surfactant and co-surfactant was varied in mass ratios 1:1, 1:2, 2:1. The different concentration ratios of oil and mixture of surfactant and co surfactant were taken as 0.5:9.5, 0.5:9, 1:9, 1:8, 1:7, 1:6, 1:5, 2:8, 3:7, 4:6 and 5:5 [18]. Ternary mixtures were formed in these ratios and then quantity of water forming transparent solution was plotted with other components in the pseudo-ternary phase diagram. Surfactant and co-surfactant got preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence then improved the stability of the formulation [19]. Co-surfactant could increase interfacial fluidity by penetrating into the surfactant film [20].

Optimization of the Formulation by Box Bhenken Design: In this study Box bhenken Statical Design was used to optimized and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the *in vitro* performance. Seventeen experiments were required for the response surface methodology on this design. The required amount of the three components (**Table 1**) and Telmisartan (20mg) and 3mg sodium hydroxide were weighed accurately and vortex for 1 minute until Drug Telmisartan was perfectly dissolve followed maintained the pH of formulation. The mixture was then gently heated at 45 - 50 °C and vortex to form homogenous mixture [21, 22]. After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the response Y_1. Optimization was performed to obtain the levels of X_1 - X_3 which maximize Y_1 at constrained conditions of Y_2 through Y_3.

TABLE 1: COMPOSITION OF SNEDDS USING BOX BEHNKEN DESIGN

Factor	Name	Units	Low Actual	High Actual
A	Oil (Labrafil M 1944 CS)	%	4.61	16.75
B	Surfactant (Kolliphor ELP: Span 80)(1:1))	%	31.07	63.78
C	Cosurfactant (PEG 400: Ethanol (1:1))	%	27.78	63.39

Quadratic Polynomial Equation:

$$Y_2 = \beta_0 + \beta_1.X_1 + \beta_2.X_2 + \beta_3.X_3 - \beta_4.X_1.X_2 - \beta_5.X_1.X_3 - \beta_6.X_2.X_3 - \beta_7.X_1^2 + \beta_8.X_2^2 - \beta_9.X_3^2$$

Preparation of Liquid SNEDDS Formulations: Formulation selected from optimized box bhenken desine for SNEDDS preparations. The required amount of the Telmisartan (20mg) were added in a accurately weighed amount of oil into a screw-capped glass vial and gently heated in a water bath at 45 - 50 ^oC the surfactant and co-surfactant were added to the oily mixture using pipette and stirred With vortex mixer for homogeneous mixing. The formulation were further sonicated for 15 min and stored at room temperature until further use. Filling the formulation into capsules. Sealing of the body and cap of capsule, either by banding or by microspray sealing [23].

Characterization of Different SNEDDS Formulation: Percentage Drug Content: Process: The drug content evaluation for the selected formulations was done by dissolving weighed amount of drug to the particular formulation. SNEDDS formulation was centrifuged diluted at

18000 rpm for 60 minutes and diluted with methanol. These drug loaded formulations were subjected to assay by analyzing it in UV spectrometer at respective 296nm λ_{max}. The percentage drug content is then calculated by the formula:

$$\% \text{ Drug content} = \frac{\text{Amount of drug in supernatant}}{\text{Initial amount of drug}}$$

Determination of Partition Coefficient: To determine the partition coefficient of the Telmisartan, the shake flask method was used; it is the classical and the most useful method of determination of partition coefficient. Briefly the procedure could be explained as excess amount of API was added in 10ml mixture of n-Octanol and water (1:1). The system was prepared in triplicate and was shaken gently in the separating funnel for 24 hours for achieving equilibrium. Then the two phases were separated and centrifuge at 8000 rpm for 20 minutes. After centrifugation, the concentration of progesterone in both phases was determined by UV spectroscopy and partition coefficient was calculated using the equation.

It can be determined by the formula:

$$K_{o/w} = C1/C2$$

Where, C1 = Conc. of solute in organic phase. C2 = Conc. of solute in aqueous phase.

$$K_{o/w} = \text{Partition coefficient}$$
$$\text{Log P} = \log (K_{o/w})$$

Thermodynamic Stability Studies: SNEDDS was subjected to thermodynamic stability studies in order to access any phase separation and stability of the prepared formulation [24, 25].

A) Centrifugation Study: The formulation was centrifuged at 18000 rpm for 30min. The resultant formulation was then checked for any instability problem, such as phase separation, creaming, or cracking.

B) Heating and Cooling Cycles: The SNEDDS formulations were subjected to six heating-cooling cycles, between 4 °C and 40 °C, for 48 h. The resultant formulations were assessed for any physical instability like precipitation and phase separation.

C) Freeze - Thaw Cycles: The SNEDDS formulations were subjected to four freeze-thaw cycles between -21 °C and 21 °C. Initially, the formulations were exposed at -21 °C in a deep-freezer for 24 h. Subsequently, the formulations were also thawed at 21 °C for 24 h and kept again in deep-freezer for the next cycle. The formulations were then observed for any physical change(s) such as phase separation and creaming.

Emulsification Study: Visual assessment was performed by drop wise addition of the pre concentrate into 100ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred on magnetic stirrer. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), non-clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours) [26].

Dilutability Test Process: The dilutability of the SNEDDS was assessed to know whether these systems would be diluted with the aqueous phase of the system without separation or not. For this purpose, selected and drug-loaded microemulsions were diluted with 900ml Distilled water and their transparency was assessed visually initial and after 24 hr [27].

***In vitro* Dissolution:** Dissolution studies were carried out for all the formulation, employing USP Apparatus 2 and 900mL of simulated gastric fluid (SGF) containing without enzyme pH 1.2, stirred at 75 RPM at a temperature of 37 ± 0.5 °C. An aliquot of sample (5mL) was periodically withdrawn at suitable time intervals. The volume was replaced with an equivalent amount of fresh dissolution medium. The samples, after suitable dilution(s), were analyzed spectrophotometrically at absorption maxima. Dissolution study was also conducted on pure in an analogous manner [28].

Cloud Point Measurement: The formulation was diluted with distilled water in the ratio of 1:100. The diluted samples were placed in a water bath and its temperature was increased gradually. Cloud point was determined as the temperature at which there was a sudden appearance of cloudiness [29, 30].

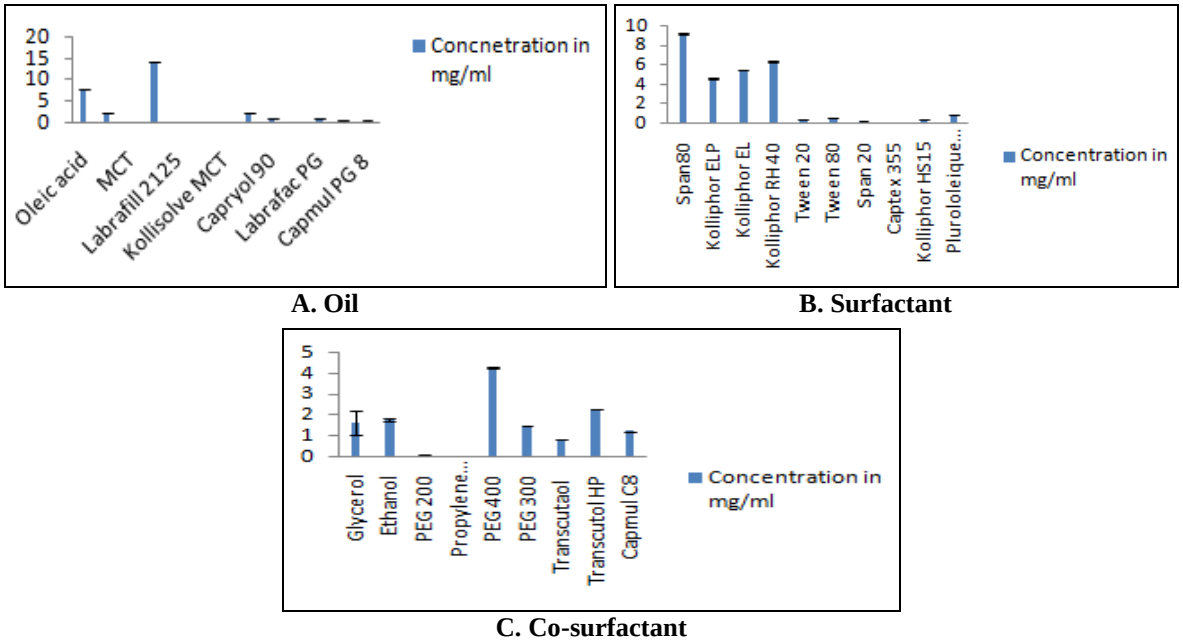
Determination of Globule Size, Zeta Potential, Polydispersity Index (PDI): Aliquots of the formulation, serially diluted with purified water, were employed to assess the globule size and zeta potential using particle size analyzer (Malvern). Zeta potential measure electric charge at the surface of particles indicates the physical stability of colloidal system it measure by zeta sizer. Each sample suitably diluted with double distilled filtered water and placed in disposable zeta cell. The zeta potential values were assessed by determining the particle electrophoretic mobility. The electrophoretic mobility was converted to the zeta potential *via* the helmholtz - smoluchowski equation, all measurement perform triplicate. The result expressed as mean ± SD.

Surface Morphology and Structure: Morphology of oil droplets in the emulsion formation was visualized with transmission electron microscope (TEM) (Hitachi, H-7500, Tokyo, Japan), operated at 80 kv ant at 50,000 times magnification. The TEM analysis also performed to visualize any precipitation of the drug upon addition of the aqueous phase. A drop of nanoemulsion after suitable dilution was allowed to deposit directly on the microscope gold coated grid and observed after drying.

Differential Scanning Calorimetry (DSC): DSC is a technique in which the difference in heat flow between the sample and a reference is recorded against temperature. All dynamic DSC studies were carried out on shimandzu thermal analyzer (TA-60 WS). A few milligram of sample, were hermetically sealed into alumunium pans and heated under under nitrogen atmosphere with the heating rate of 10 °C/ min.

RESULT AND DISCUSSION:

Solubility of Telmisartan (Drug) in Various Solvents Oils: Lipid based compounds forms a possible platform for improving oral bioavailability of drug belonging to BCS class II and IV for formulation of SNEDDS log p value should be high [31, 32]. Drug loading capacity of SNEDDS formulations depends on the solubility of drug in the various vehicles of the system which was determined by solubility studies. The use of long chain triglycerides oil which leads to the increased lymphatic transport used to enhance oral bioavailability. The components in the formulation (**Fig. 1**) of SNEDDS were selected to have maximum solubility for drug along with good miscibility with each other to produce a stable formulation. The solubility of Telmesartan in oil (**Fig. 1A**) found best in labrafill 1944, oleic acid, and ethyl oleate. In surfactants (**Fig. 1B**) kolliphour EL, kolliphour RH40, kolliphour ELP, Span 80 and cosurfactant (**Fig. 1C**) Transcutol HP, PEG - 400, Ethanol, Transcutol P, Glycerol shows good solubility to drug Telmisartan. Thus these oils, surfactants and co-surfactants are selected for further screening.



A. Oil **B. Surfactant**

C. Co-surfactant

FIG. 1: SOLUBILITY OF TELMISARTAN (DRUG) IN A) OILS, B) SURFACTANTS, C) CO-SURFACTANTS

Screening of Surfactants and Co-Surfactants:

Screening of Surfactants: Percent transmittance for surfactant (**Table 2**) was highest in Kolliphor EL+ Span 80 (1:1) 85.33 ± 0.05, Kolliphor RH40+Span 80 (1:1) 81.4 ±0.994, and Kolliphor ELP + Span 80 (1:1) 87.7 ± 0. They were also observed for turbidity or phase separation visually.

TABLE 2: PERCENT TRANSMITTANCE (% T) OBSERVATIONS FOR SURFACTANTS

Oil / surfactant	Span 80	Kolliphor EL	Kolliphor RH 40	Kolliphor ELP	Kolliphor EL + Span 80 (1:1)	Kolliphor RH40 + Span 80 (1:1)	Kolliphor ELP +Span 80 (1:1)
Oleic acid	3.86±0.05	4.76±0.15	18.1±0.86	2.93±0.11	-	-	-
Ethyl oleate	60.33±0.05	54.2±0.1	13.1±0.1	38.36±0.25	-	-	-
Labrafill 1944	73.83±2.38	78.4±0.06	80.4±0.17	82.36±0.05	85.33±0.05	81.4±.994	87.7±0

Screening of Co-Surfactants:

TABLE 3: PERCENT TRANSMITTANCE (% T) OBSERVATION FOR CO-SURFACTANT

S. no	Oil	Surfactant	Co-surfactant	% Transprancy of 24 Hrs
1	Labrafill 1944	Kolliphor RH40 + Span 80 (1:1)	Glycerol	Bluish Transparent
2	Labrafill 1944	Kolliphor RH40 + Span 80	PEG400	Bluish Transparent
3	Labrafill 1944	Kolliphor ELP + Span 80(1:1)	Ethanol	Bluish Transparent
4	Labrafill 1944	Kolliphor ELP + Span 80 (2:1)	PEG400	Bluish Transparent
5	Labrafill 1944	Kolliphor ELP: Span 80 (1:1)	PEG400:Ethanol (1:1)	Transparent
6	Labrafill 1944	Kolliphor ELP: Span 80 (2:1)	PEG400:Ethanol (1:1)	Transparent

Pseudoternary Phase Diagram: Self-emulsifying systems required very low free energy to form emulsion hence spontaneous formation of an interface between oil droplets and water. On the basis of pseudo ternary phase diagram (**Fig. 2**) Labrafil 1944 kolliphor ELP: Span 80 (1:1) PEG 400: Ethanol (1:1) has higher area of emulsifying area. Therefore selected combination studied further.

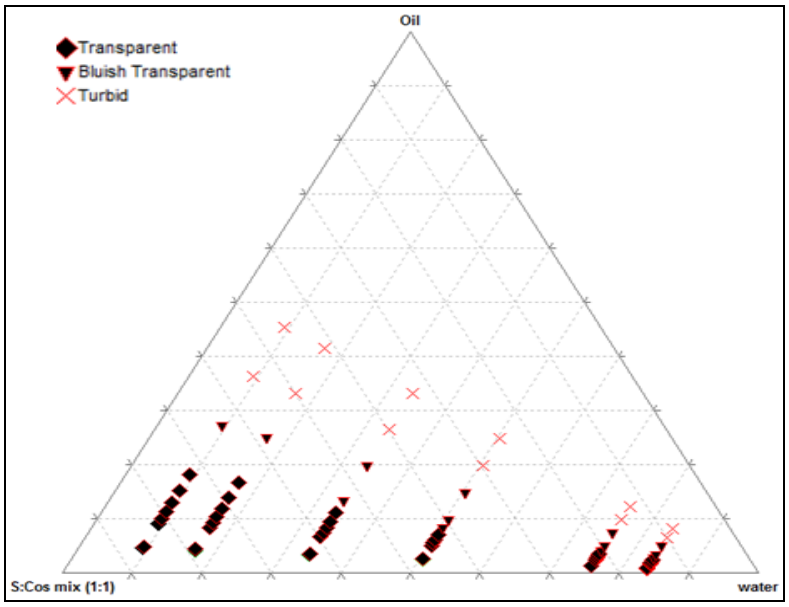
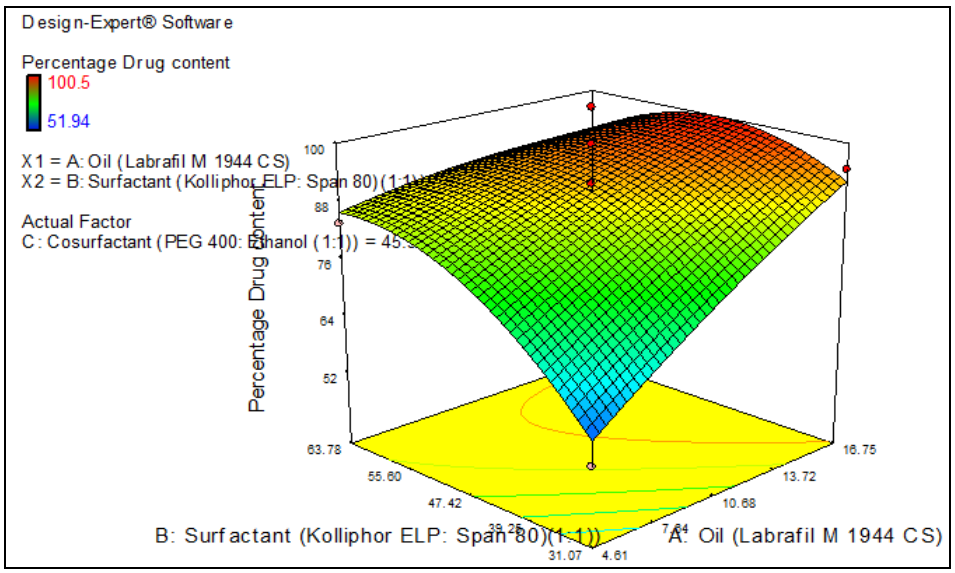


FIG. 2: PSEUDOTERNARY PHASE DIAGRAM

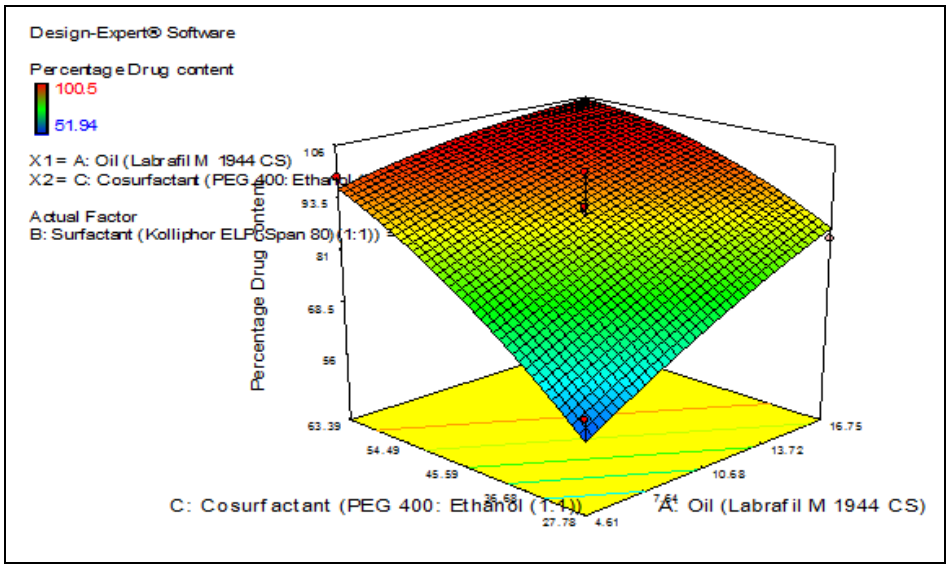
Optimization Through Box Bhenken Desine:

TABLE 4: COMPOSITION OF SNEDDS USING BOX BEHNKEN DESIGN

Factor	Name	Units	Low Actual	High Actual
A	Oil (Labrafil M 1944 CS)	%	4.61	16.75
B	Surfactant (Kolliphor ELP: Span 80) (1:1))	%	31.07	63.78
C	Co-surfactant (PEG 400: Ethanol (1:1))	%	27.78	63.39



3D SURFACE RESPONSE GRAPH BETWEEN OIL (X_1), SURFACTANT (X_2) WITH % ENTRAPMENT (Y_1)



3D SURFACE RESPONSE GRAPH BETWEEN OIL (X_1), CO - SURFACTANT (X_3) WITH % ENTRAPMENT (Y_1)

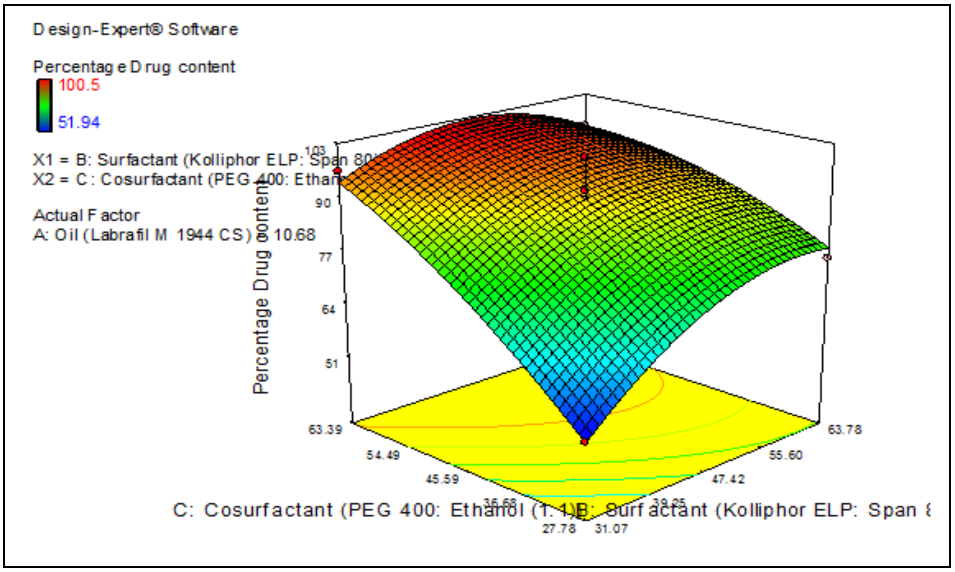


FIG. 3: 3D SURFACE RESPONSE GRAPH BETWEEN SURFACTANT (X_2), CO-SURFACTANT (X_3) WITH % ENTRAPMENT (Y_1)

TABLE 5: OPTIMIZED CONCENTRATION OF DEPENDENT VARIABLES

Oil (labrafill M) 1944CS	Surfactant (Kolliphor ELP: SPAN 80) (1:1)	Co-surfactant (PEG400: ethanol (1:1))	Percentage drug content	Formulation code
6.78	50.09	59.65	93.217	A2
15.01	55.23	29.09	86.269	A5
16.34	40.84	44.36	97.314	A8

The selected optimized formulations were further evaluated.

Evaluation of Different SNEDDS Formulation:

Percentage Drug Content:

TABLE 6: PERCENTAGE DRUG CONTENT

Number	Oil (Labrafil M 1944 CS)	Surfactant (Kolliphor ELP: Span 80) (1:1))	Co-surfactant (PEG 400: Ethanol (1:1))	Percentage Drug content
A2	6.78	50.09	59.15	96.99352396
A5	15.01	55.23	29.09	86.26918312
A8	16.34	40.84	44.36	97.31484378

Thermodynamic Stability Studies:

Centrifugation Study:

TABLE 7: CENTRIFUGATION STUDY

Formulation code	Appearance
A2	Homogenous, no phase separation
A5	Homogenous, no phase separation
A8	Homogenous, no phase separation

Heating and Cooling Cycles: The SNEDDS formulations were subjected to six heating-cooling cycles, between 4 °C and 40 °C, for 48 h. The resultant formulations were assessed for any physical instability like precipitation and phase separation.

Freeze - Thaw Cycles: The SNEDDS formulations were subjected to four freeze-thaw cycles between -21 °C and 21 °C. Initially, the formulations were exposed at -21 °C in a deep-freezer for 24 h. Subsequently, the formulations were also thawed at 21 °C for 24 h and kept again in deep-freezer for the next cycle. The formulations were then observed for any physical change(s) such as phase separation and creaming.

TABLE 8: HEATING COOLING CYCLE AND FREEZE - THAW CYCLE

S. no	Formulation code	Heating and cooling cycles	Freeze-Thaw Cycles
1	A5	Homogenous and no phase separation	Homogenous and no phase separation

Emulsification Study:

TABLE 9: EMULSIFICATION STUDY

Formulation code	Percentage Transmittance std	Emulsification time (Seconds)	Appearance	Appearance after 24 hr.
A2	98±1.41	Within 10 seconds	Transparent	Turbid
A5	99.5±0.70	Within 10 seconds	Transparent	Transparent
A8	97±1.41	Within 10 seconds	Transparent	Bluish Transparent

***In vitro* Dissolution:** The samples, after suitable dilution(s), were analyzed spectro-photometrically at absorption maxima 296nm.

Dissolution study was also conducted on Marketed tablet Telvas (Telmisartan tablet IP 20mg, Aristo,) in an analogous manner.

TABLE 10: PERCENTAGE DRUG RELEASE OF MARKETED PREPARATION AND SNEDDS FORMULATION A5

Time (min.)	Percentage Drug release of Marketed Preparation Telvas ± Std.	Percentage Drug release of Formulation A5 ± Std.
1	0.72±0.04	0.86±0.03
3	1.02±0.06	18±1.0
5	1.36±0.05	56.13±0.16
8	1.83±0.06	82.26±1.32
10	2.07±0.08	94.57±0.82
15	5.82±0.48	93.75±0.99
20	9.87±1.70	93.75±1.65
25	11.48±1.13	93.395±2.48
30	14.26±1.681	93.98±0.99

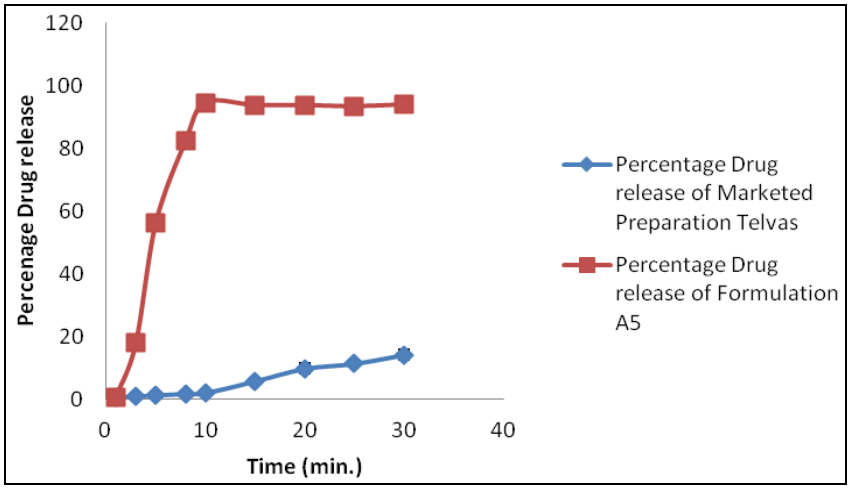


FIG. 4: PERCENTAGE DRUG RELEASE OF MARKETED PREPARATION AND FORMULATION A5

From above **Fig. 4** it was found that Formulation F5 showed fast drug release as compare to marketed preparation.

Dilutability Test Process: On the basis of above evaluation Parameter (**Table 11**) Formulation A5 was selected for further evaluation parameter.

TABLE 11: DILUTABILITY TEST PROCESS

In Water 100ml				
Formulation code	**Percentage Transmittance**	**Emulsification time (Seconds)**	**Appearance**	**Appearance after 24 hr**
A2	Turbid	Within 10 seconds	Turbid	Turbid
A5	99.5±0.42	Within 10 seconds	Transparent	Transparent
A8	65.45±4.31	Within 10 seconds	Bluish Transparent	Bluish Transparent
		In 0.1N HCl 100ml		
Formulation code	Percentage Transmittance	Emulsification time (Seconds)	Appearance	Appearance after 24 hr
A2	Turbid	Within 10 seconds	Turbid	Turbid
A5	100±0.14	Within 10 seconds	Transparent	Transparent
A8	98.4±0.42	Within 10 seconds	Bluish Transparent	Bluish Transparent
		In Water 900ml		
Formulation code	Percentage Transmittance	Emulsification time (Seconds)	Appearance	Appearance after 24 hr
A2	Turbid	Within 10 seconds	Turbid	Turbid
A5	95.25±3.18	Within 10 seconds	Transparent	Transparent
A8	93.8±1.27	Within 10 seconds	Bluish Transparent	Bluish Transparent
		In 0.1 N HCl 900ml		
Formulation code	Percentage Transmittance	Emulsification time (Seconds)	Appearance	Appearance after 24 hr
A2	Turbid	Within 10 seconds	Turbid	Turbid
A5	100.05±0.212	Within 10 seconds	Transparent	Transparent
A8	99.7±0.28	Within 10 seconds	Bluish Transparent	Bluish Transparent

Cloud Point Measurement: The cloud point (**Table 12**) of A5 SNEDDS was found to be 62.65 ± 1.42 indicating the formed nanoemulsion at the physiological temperature will be a stable one.

TABLE 12: CLOUD POINT MEASUREMENT OF DRUG CONTAINING SNEDDS

S. no.	Formulation Code	Cloud Point
1	A5	62.65±1.42

Determination of Globule Size, Zeta Potential and Poly Dispersity Index:

TABLE 13: FORMULATION A5 PARTICLE SIZE, PDI, ZETA POTENTIAL

S. no.	Formulation Code	Particle Size (nm)	PDI	Zeta Potential (mV)
1	A5	164.9	0.228	-26.0

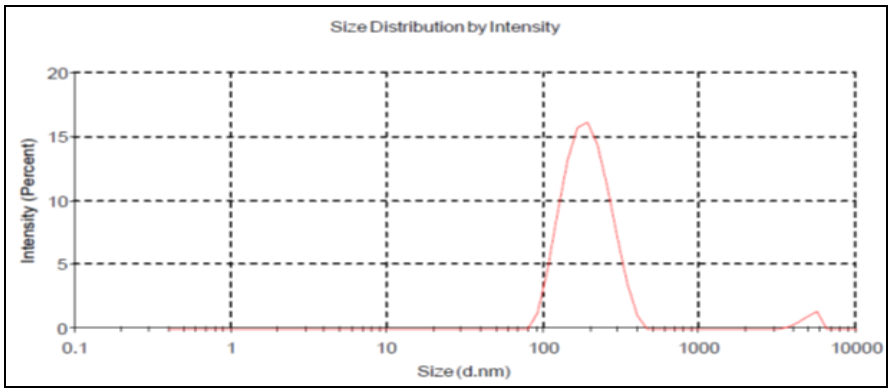


FIG. 5: GRAPH OF PARTICLE SIZE OF A5 FORMULATION

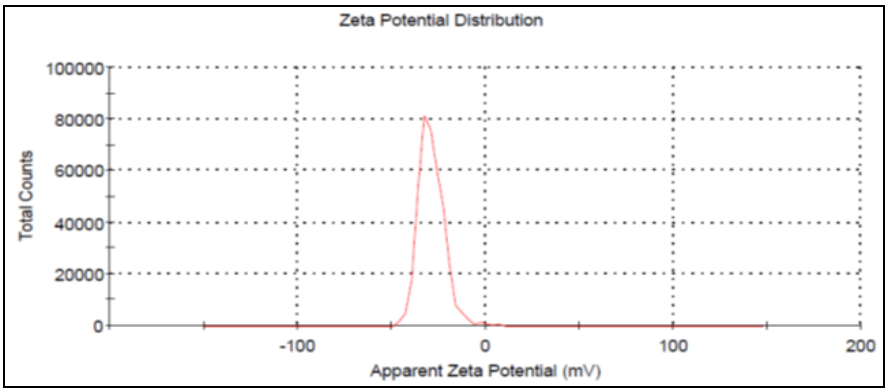


FIG. 6: GRAPH OF ZETA POTENTIAL OF A5 FORMULATION

Tem Images of A5 Drug Loaded SNEDDS Formulation: From TEM images **Fig. 7** of formulation showed uniform spherical nanoemulsion droplets. Thermodynamic stability study.

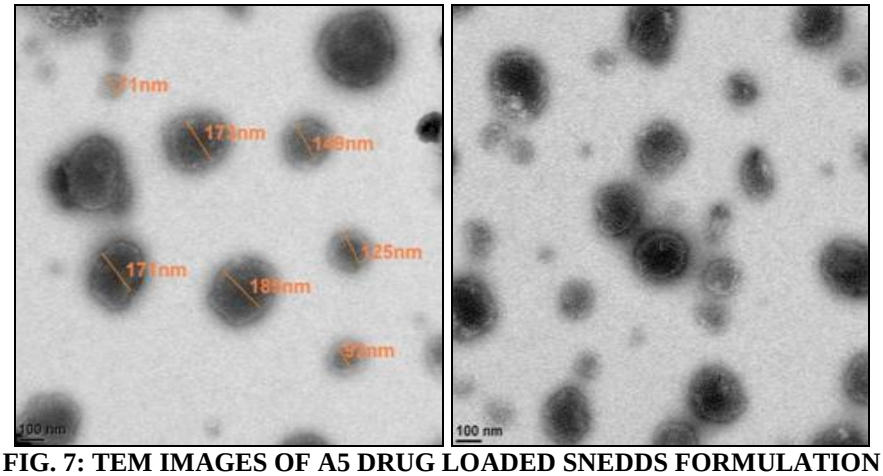
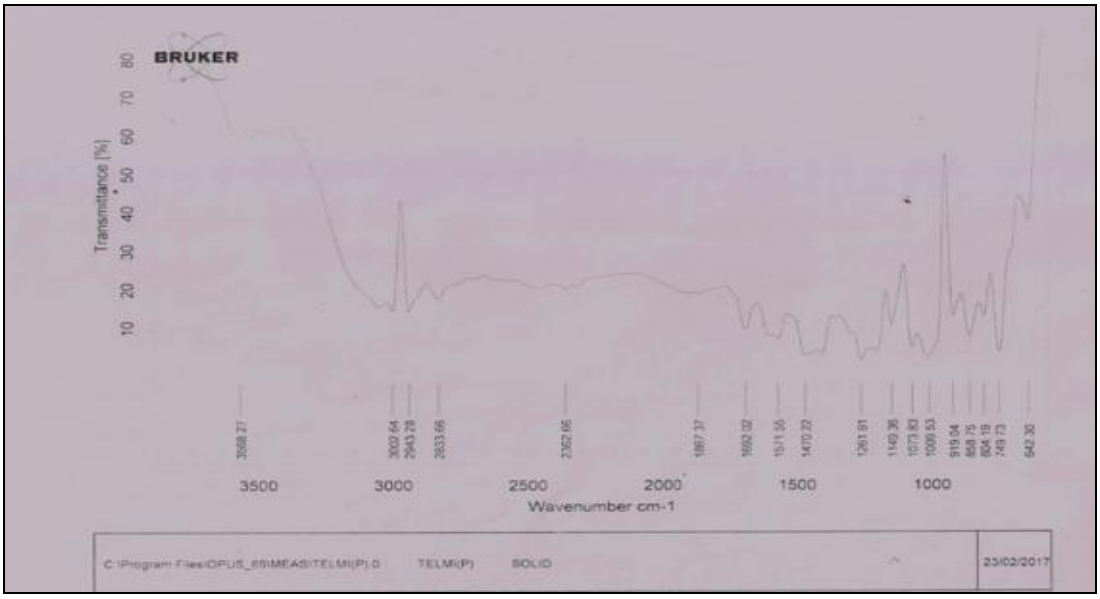


FIG. 7: TEM IMAGES OF A5 DRUG LOADED SNEDDS FORMULATION

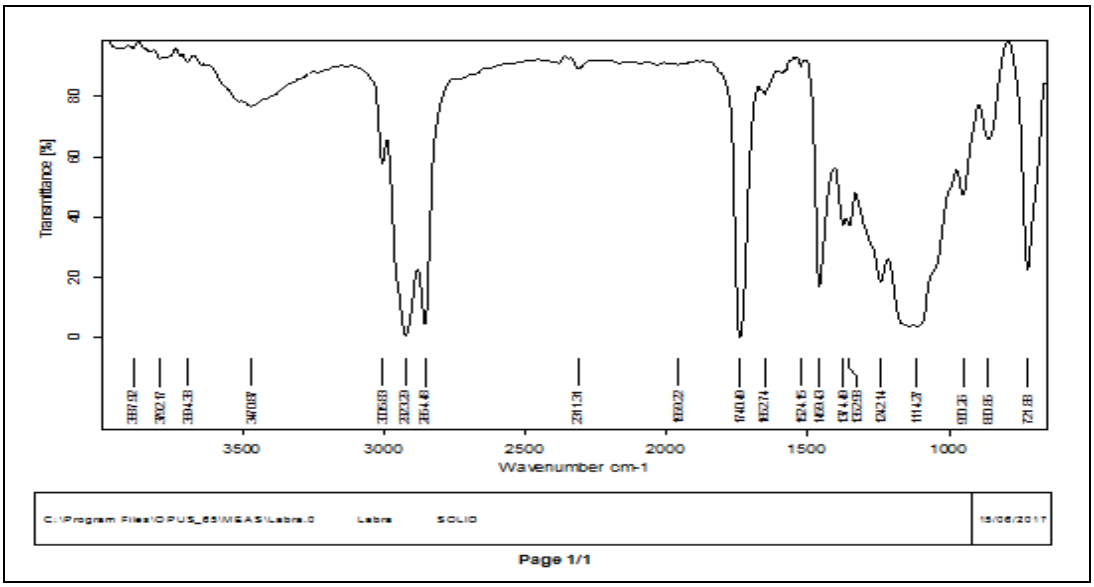
FTIR Study: The FTIR spectrum (**Fig. 8**) of physical mixture and optimized formulation displayed peaks of drug with some minor displacements. FT-IR analysis of optimized formulation and the drug were studied for the interaction of the excipient and the drug in the final formulation. Telmisartan has characteristic absorption peaks (**Table 14**) C-H at 3022.64cm^{-1}, carboxylic acid at 1702 cm^{-1}, C-C at 1571.55 cm^{-1}, 1, 2- distributed benzene ring vibration at 749.73cm^{-1}.

Similar peaks were observed in spectra of different combinations of excipient and in optimized formulation (SNEDDS), along with interfering peaks indicating there is no unwanted reaction between Telmisartan and other excipient used in the study. From the figure and table it can be inferred that there is no unwanted reaction between Telmisartan and other excipient used in the study. From the figure and table it can be inferred that there was no appearance or disappearance of any characteristic peaks. This shows that there was no interaction between the drug and the excipient used in the SNEDDS preparation.

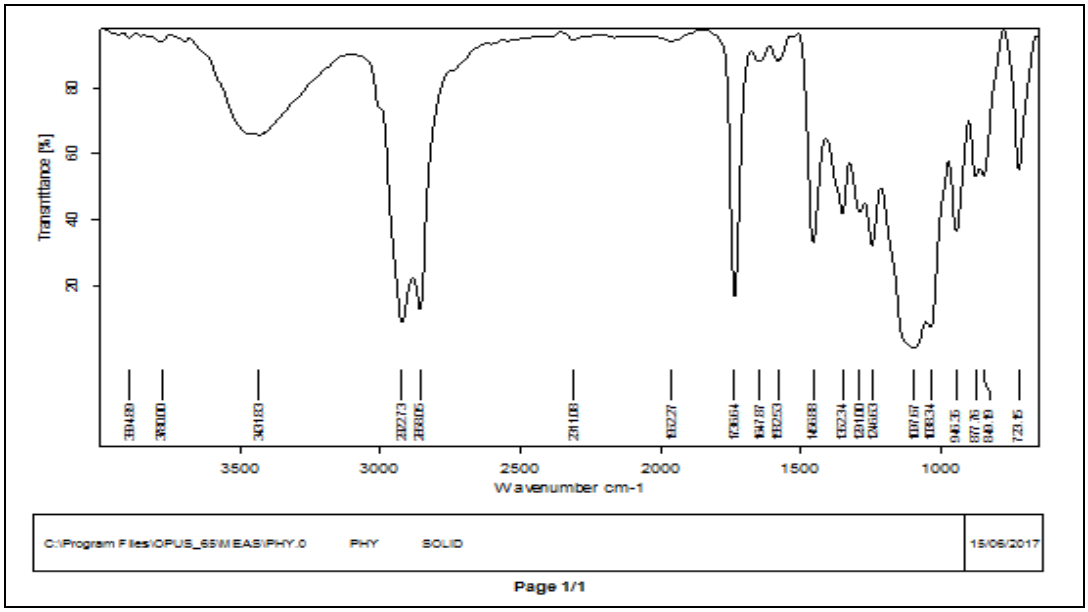
Partition Coefficient: The partition coefficient of drug is 3.01 ± 1.68. So the drug is lipophillic in nature.



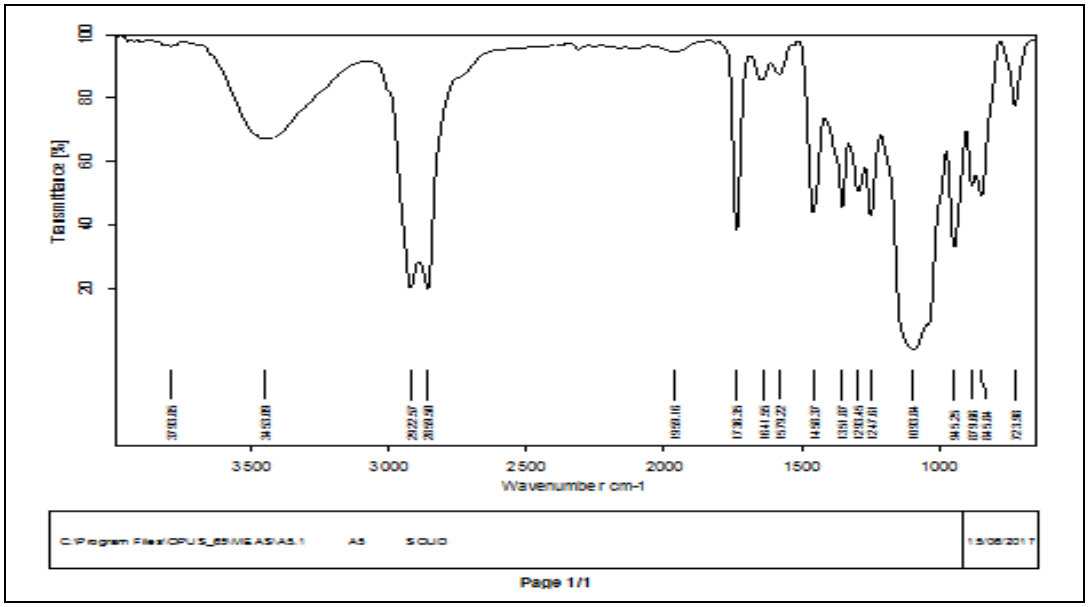
A) FTIR SPECTRA OF TELMISARTAN DRUG



B) FTIR SPECTRA OF LABRAFIL OIL



C) FTIR SPECTRA OF PHYSICAL MIXTURE OF DRUG, OIL, SURFACTANT AND COSURFACTANT



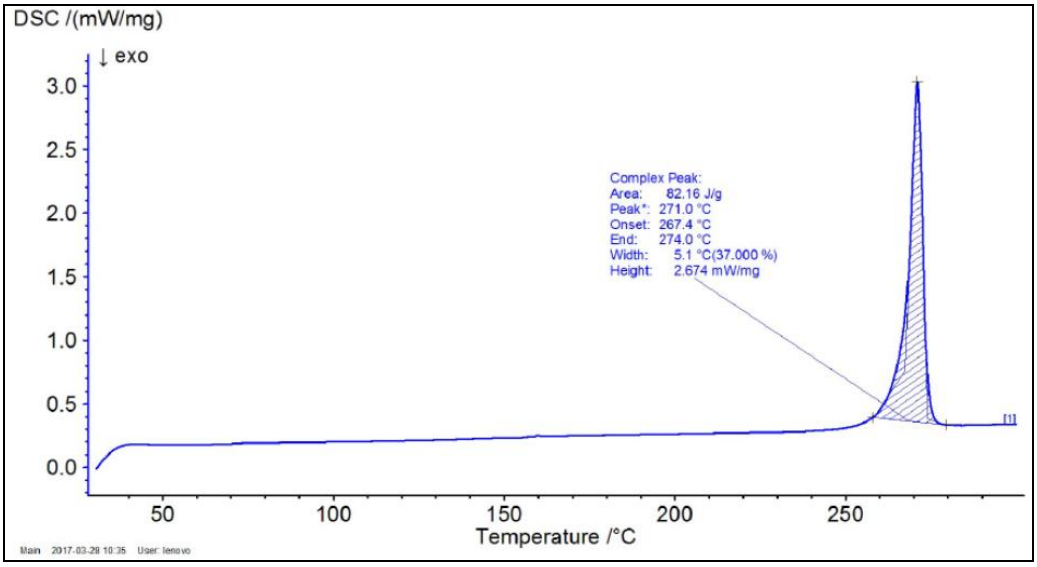
D) FTIR SPECTRA OF OPTIMIZED FORMULATION A5

FIG. 8: FTIR SPECTRA OF A) TELMISARTAN DRUG B) LABRAFIL OIL C) PHYSICAL MIXTURE OIL, SURFACTANT CO-SURFACTANT D) OPTIMIZED FORMULATION A5

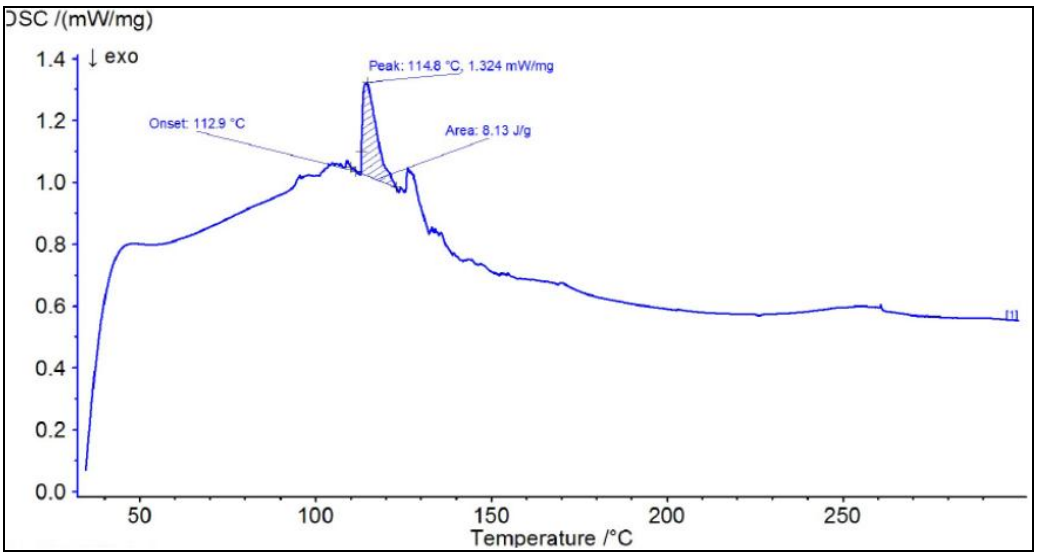
TABLE 14: FTIR OF DRUG, PHYSICAL MIXTURE AND FORMULATION A5

S. no.	Functional group	Observed peak (cm^{-1}) in Drug	Observed peak (cm^{-1}) of Drug in Physical mixture	Observed peak (cm^{-1}) of drug in formulation A5
1	Aromatic C- H stretch	3022.64	-	-
2	Carboxylic acid	1702	-	-
3	Aromatic C - C bending and stretching	1571.55	1562.53	1579.22
4	1, 2-disubstituted benzene ring vibrations	749.73	723.15	723.96

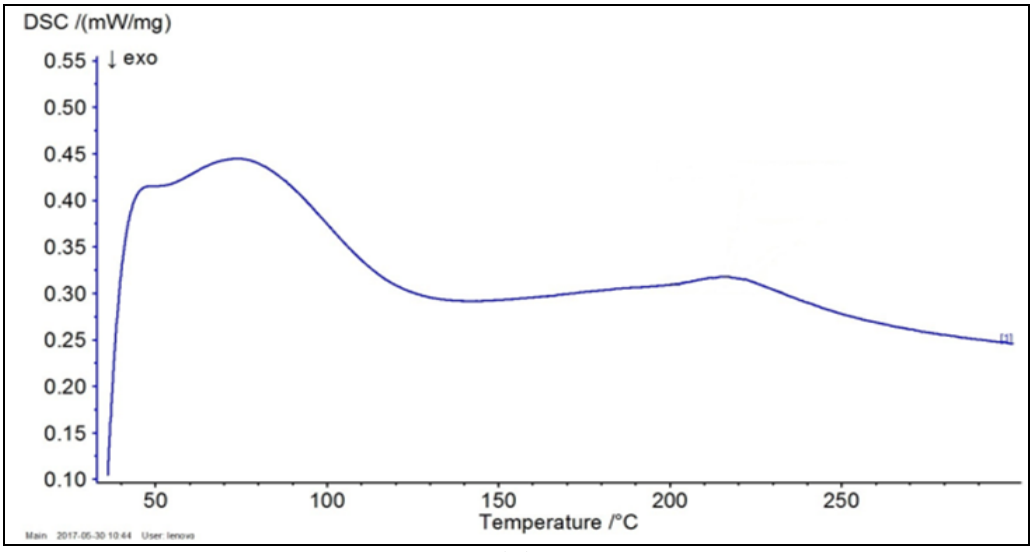
Differential Scanning Calorimetry (DSC): From above DSC thermogram Melting point of drug Telmisartan was found to be 267.4 - 274 °C. No exothermic peaks were found in the optimized formulations indicating that Telmisartan must be molecularly dissolved in an amorphous state in the formulation.



(A)



(B)



(C)

FIG. 9: DSC THERMOGRAM A) DRUG TELMISARTAN B) PHYSICAL MIXTURE DRUG OIL SURFACTANT C) FORMULATION A5

CONCLUSION: Result suggested that self nano emulsifying drug delivery system (SNEDDS) of temisartan may be prepared by using appropriate oil, in proper ratio and kind of surfactant and co-surfactant within the desired particle size range, the amount of drug released that could increased the bioavailability of Telmisartan.

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