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DEVELOPMENT AND EVALUATION OF SOLID SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF POORLY SOLUBLE OLMESARTAN MEDOXOMIL BY USING ADSORPTION ON TO SOLID CARRIER TECHNIQUE

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Keywords:

Olmesartan Medoxomil, Solid self-Nanoemulsifying drug delivery system, Adsorption, Dissolution

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ABSTRACT: Olmesartan medoxomil (OLM) is an angiotensin II receptor blocker antihypertensive agent. It is a highly lipophilic (log p (octanol / water) 5.55), poorly water soluble drug with absolute bioavailability of 26%.The present work aimed at formulating a solid self Nano emulsifying drug delivery system (solid-SNEDDS) for Olmesartan Medoxomil with the objective of improving the aqueous solubility, dissolution and oral delivery of the drug. The solubility of OLM was determined in various vehicles like oils, surfactants and co-surfactants. Pseudoternary phase diagrams were constructed for excipients to identify the efficient self-emulsifying region and proportions of various compatible excipients for the formulation. The liquid SNEDDS was a system that consists of Olmesartan, Labrafil m1944 CS, and Tween 80, Polyethylene glycol 400 as a drug, oil, surfactant and co-surfactant. The optimized liquid SNEDDS was transformed into a free flowing powder by using Neusilin US2 as adsorbent. Prepared SNEDDS formulations were tested for nanoemulsifying properties and the resultant nanoemulsions were evaluated for robustness to dilution, assessment of efficiency of self emulsication, emulsification time, turbidity measurement, drug content and *in-vitro* dissolution. The optimized Solid-SNEDDS formulation further evaluated for heating cooling cycle, centrifugation studies and freeze thaw cycling, particle size distribution, zeta potential were carried out to confirm the stability of the formed Solid-SNEDDS. The formulation was found to show a significant improvement in terms of the drug release with complete release of drug within 60 min is selected as optimized SNEDDS formulation. The dissolution of the drug was enhanced significantly from the SNEDDS formulation as compared to plain drug.

INTRODUCTION: Most of the new chemical entities (NCE) developed currently are slightly soluble in Aqueous media and with poor bioavailability.

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The properties of NCEs are changing towards higher molecular weight and high lipophilicity resulting in low aqueous solubility.

Various formulation methods have been developed to increase the solubility and there by bioavilability of drugs, these methods includes, particle size reduction [1], pH adjustment, co-solvency, complexation, solid dispersions, SEDDS *etc*. SEDDS are having that potential to enhance the solubility of hydrophobic and lipidic drugs and they consist of mixtures of an oily vehicle,

surfactants, and cosurfactants. Selection of suitable SEDDS formulation depends on (1) Solubility of Olmesartan in various excipients (2) Self-emulsifying region in the phase diagram (3) self-emulsification time (4) Emulsion Droplet size and Zeta potential distribution of emulsion (5) thermodynamic stability of emulsion.

Olmesartan medoxomil (OLM) is a angiotensin II receptor blocker, non peptide used to treat Hypertension. Olmesartan is Ester-type pro-drug that is esterified during or after its absorption in gastrointestinal tract. Olmesartan has poor aqueous solubility and is ≤1 mg/ml. oral administration, with a bioavailability approximately 26% which is suitable for SNEDDS Method.

MATERIALS AND METHODS:

Materials: Olmesartan medoxomil Gift samples from NATCO company, Labrafil M 1944 CS, Labrafac Lipophile WL 1349, Capryol 90, Castor oil, Peceol, Capmul PG-8, Lauroglycol 90, Captex 200, Labrasol, Oleic acid, Tween 80, Cremophore RH 40, Propylene glycol, Transcutol HP, Polyethylene glycol 400 (PEG 400), Methanol, Potassium bromide, Hydrochloric acid, Neusilin, Capsules.

Methods:

Solubility Studies: [2, 3] Solubility studies were carried by placing an excess quantity of Olmesartan in a screw capped vials containing 1 g of vehicles (oils, surfactants and co-surfactants). The suspensions of excipients were heated on a water bath at 40 °C to increase the solubilization using vortex mixer. The suspensions were constantly agitated on a Rotary shaker for 48 h at ambient temperature. After reaching equilibrium the suspensions were centrifuged at 5000 rpm for 20 min and the supernatant was separated and filtered through 0.45 µm Membrane filters. The filtrates are suitably diluted with solvent and analyzed spectrophotometrically for the dissolved drug at 257 nm. Methanol is used as blank for the photometric determination of solubility of samples. Concentration of Olmesartan in each of the vehicle was calculated from calibration curve.

Construction of Pseudo-Ternary Phase Diagrams: [2, 3] Pseudo-ternary phase diagrams were constructed to determine the appropriate ratios for selected vehicles like oil, surfactant, and co-surfactant with water at Room Temperature by Water titration method. The surfactant (Tween 80) and co-surfactant (PEG 400 / Propylene glycol) id mixed in ratio 4:1, 1:4, 3:1, 2:1 and 1:1 respectively. Aliquots of S_{mix} were mixed with oil (Labrafil M 1944 CS) at Different ratios like 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 in different vials and Titrated with water and note down the weight of water on each addition at room Temperature.

The samples were kept side for 30 sec and Observe visually after each addition of water. Based on the visual observation the formed emulsions were classified as nano, micro and coarse Emulsions and gel systems. Pseudo ternary phase diagrams were Plotted using Triplot software version 4.1.2. The samples which were Clear and Bluish transparent in appearance were considered as nano and micro emulsions.

Formulation of Liquid SNEDDS: [4, 5, 6] A Number of SNEDDS formulations were prepared with different ratios of oil, surfactant and co-surfactant. A single dose of OLM (20 mg) was incorporated in all formulations. The final weight of the Formulations was kept at 500 mg. The mixtures were prepared by dissolving the drug in oil and by addition of surfactant and co surfactant in glass vials. The resulting mixtures were mixed continuously by vortex mixer followed by sonicate it for few minutes to obtain a homogenous isotropic mixture.

TABLE 1: FORMULA OF SELECTED SELF-EMULSIFYING FORMULATIONS

S. no.	Formulation Name	Drug (mg)	Labrafil M 1944 CS (mg)	Tween 80 (mg)	PEG400 (mg)	Propylene Glycol (mg)
1	LMTPEG41-1	20	48	345.6	86.4	-
2	LMTPEG31-2	20	96	288	96	-
3	LMTPG41-2	20	96	307.2	-	76.8
4	LMTPEG41-4	20	192	246.4	61.6	-
5	LMTPG31-2	20	96	288	-	96

Formulation of Solid- Self Nano Emulsifying Drug Delivery System: [7, 8, 9]

Adsorption to Solid Carriers: Free flowing powder systems may be obtained from liquid SNEDDS formulations by adsorption into solid carriers. The adsorption process involves addition of the liquid formulation onto carrier by mixing in a blender. The resultant free flowing powder filled directly into the capsules. Benefit of the adsorption technique is good content uniformity. SNEDDS can be adsorbed onto suitable Solid carriers such as Neusilin. Solid - SNEDDS were prepared by mixing the liquid SNEDDS containing Olmesratn with Neusilin in 1:2 proportions. In brief liquid SNEDDS was added progressively over the carrier in a mortar. After every addition, mixture was blended vigorously and homogenized to make sure uniform distribution of the formulation. Resulting damp mass was passed through the sieve no. 120 and dried at room temperature and store it for further use.

Characterization of SNEDDS: [10, 11, 12, 13]

Self Emulsification and Visual Evaluation: The prepared emulsions were added drop wise into 250 ml of water. Self emulsifying mixtures will be quickly disperse in water on mild shaking and observe the formed emulsion by visually.

Dispersibility Test: The Time taken for the development of Nano emulsion was determined by drop wise adding of 1g of formulation into 250 ml of distilled water, simulated gastric fluid and phosphate buffer of pH 6.8 in separate glass beakers at 37.5 ºC. The contents were mixed using Magnetic stirrer at 100 rpm. The affinity to form an emulsion was assessed as "good" when the emulsification occurs rapidly less than 1 min with Clear or Transparent appearance. The tendency to form an emulsion was assess as "bad" when there is less clear emulsion formation. Based on visual appearance and time taken for self emulsification, formulations are graded as:

Grade I: Rapidly forming (In 1 min) Nano emulsion having a Clear (or) Bluish appearance.

Grade II: Rapidly forming, slightly less Clear emulsion, having a Bluish white appearance.

Grade III: Fine Milky emulsion is formed within 2 min.

Grade IV: Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify (More than 2 min).

Phase Separation and Stability Study of Emulsions: Each of the formulation (50 µl) was added to a vials containing 5 ml of double distilled water, simulated gastric fluid at room Temperature and cyclo mixed for 1 min and then each mixture was stored and observed for phase separation and precipitation of drug at intervals 2, 4, 6, 8, 12, 24 h period of time.

Effect of Dilution: formulations were subjected to dilution in different ratios of 1:10, 1:50, 1:100 and 1:1000 fold dilution with distilled water, Simulated gastric fluid (pH 1.2) and phosphate buffer (pH 6.8). The diluted preparations were stored for 24 h and observe for any changes like precipitation or phase separation.

Percentage (%) Transmittance: Each formulation (100 µL) was added to a vial containing 10 mL of Double distilled water, 0.1 N HCl and phosphate buffer of pH 6.8 at room temperature and cyclomixed it for 1minute. Each of the samples was observed for % Transmittance at 257 nm.

Drug Loading Efficiency: The quantity of drug present in the formulation was determined UV Spectrophotometrically. 40 mg of formulations was accurately weighed and dilute it with 100 ml of methanol. Resulting solutions were analyzed spectrophotometrically after suitable dilution. Drug loading efficiency was calculated by Following Formula:

$$\text{Drug loading efficiency} = \frac{\text{Amount of drug in known amount of formulation} \times 100}{\text{Initial drug load}}$$

FT-IR Studies (Compatibility Studies): FT-IR spectra of pure drug and drug-excipients were obtained by FT-IR Spectrophotometer (Bruker-Alpha). The spectra of drug, excipients and Formulation were taken with the accumulation 24 scans and a resolution of 4 cm^{-1} over the range of 400 - 4000 cm^{-1}. The spectra of drug-excipient mixtures so obtained were compared with spectra of pure drug for any Incompatibilities.

Thermodynamic Stability Studies: The physical stability of a SNEDDS formulation is very important for its performance during its storage and usage it can be adversely affected by precipitation of drug in excipient medium. Poor physical stability of formulation can lead to phase separation of the excipients which in turn affect bioavailability their by therapeutic efficiency. The following cycles were carried out for these studies

Centrifugation: In order to estimate Meta stable systems, the optimized SNEDDS formulations were diluted with 100 times with distill water. Which pass heating - cooling cycle are centrifuged it at 3500 rpm for 30 min. Those formulations that do not show any physical separation are chosen for the freeze thaw test.

Freeze Thaw Cycle: This test was performed for accelerate stability testing of nano-emulsion formulations. In this study three freeze thaw cycle of formulations were exposed between temperatures -20 ºC and +25 ºC for each temperature cycles not more than 48 h after 48 h samples were observed for phase separation (or) precipitation. Those formulations which showed the maximum stability were selected for more study.

***In-vitro* Drug Release Study:** [14] The *in-vitro* dissolution study of SNEDDS were performed by filling the formulations in suitable size capsules and carried out using USP-Type II dissolution test apparatus (DS8000 Lab India) in 900 mL of 0.1N HCl (pH 1.2) at 37 ± 0.5 ºC with 100 rpm rotating speed. *In-vitro* drug release study was performed for 90 min in 0.1N HCl. 5 ml of Sample were withdrawn for each time intervals at 0, 5, 10, 15, 20, 30, 45, 60, 75, 90 min time intervals and filtered through the 0.45 µ filter. An equal amount of fresh dissolution medium was replaced after every sampling to maintain required volume. Samples were analyzed by using UV-Spectro-photometer at 202 nm. Percentage drug release and cumulative percent of drug release were calculated from absorbance and concentration that were obtained with the help of standard graph of Olmesartan.

Droplet Size (d.nm) and Zeta Potential (mV) Determination: [15, 16] Prepared SNEDDS formulations were diluted upto 100 times with Double distilled water in a beaker with constant stirring on a magnetic stirrer. The emulsion droplet size and Zeta potential were determined after 1 h by Dynamic Light Scattering (DLS) spectroscopy using a Zetasizer Nano ZS Version 6.20 (Malvern Instruments). Size determination was performed at 25 ºC by placing in an electrophoretic cell with an angle of detection of sample at 90 ºC for measurement.

RESULTS AND DISCUSSION: Determination of λ_{max} and Calibration Curve of Olmesartan Medxomil in Methanol:

The drug shows an absorption maximum in Methanol at 257 nm. A linear correlation between the λ max and the concentration of Olmesartan was established over the examined concentration range (2 - 10 µg/ml). Linear regression data are given below (R^2 = 99056).

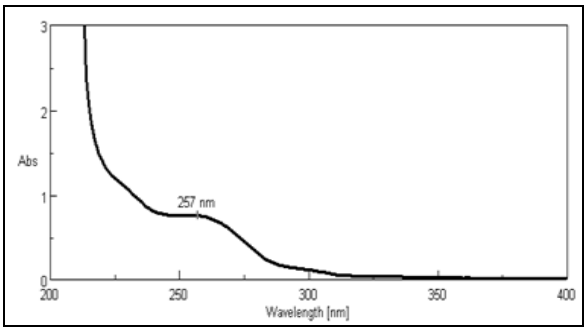

FIG. 1: UV ABSORPTION SPECTRUM OF OLMESARTAN IN METHANOL

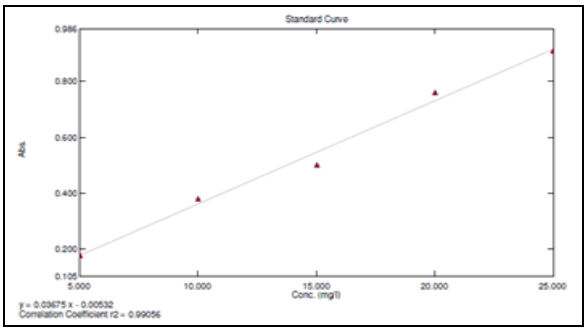

FIG. 2: STANDARD GRAPH OF OLMESARTAN IN METHANOL

Determination of λ_{max} and Calibration Curve of Olmesartan Medxomil in 0.1N HCl: The drug shows an absorption maximum in 0.1N HCl at 202 nm. A linear correlation between the λ_{max} and the concentration of Olmesartan was established over the examined concentration range (2 - 10 µg/ml). Linear regression data are given below (R^2 = 99088).

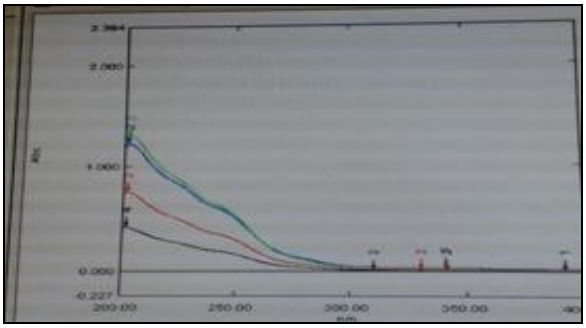

FIG. 3: UV ABSORPTION SPECTRUM OF OLMESARTAN IN 0.1N HCl

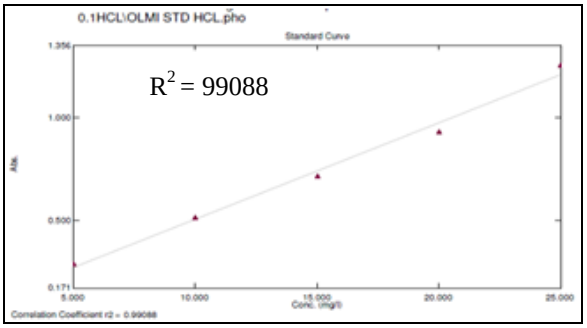

FIG. 4: STANDARD GRAPH OF OLMESARTAN IN 0.1N HCl

Solubility Studies: [8, 9]

TABLE 2: SOLUBILITY OF OLMESARTAN MEDOXOMIL IN DIFFERENT OILS

Oil	Concentration (mg/ml)
Labrafil M 1944CS	31.675
Ground nut oil	25.928
Capmul pg8	17.708
Captex200	13.127
Capryol	9.803
Labrafac lipophile 1349	3.716

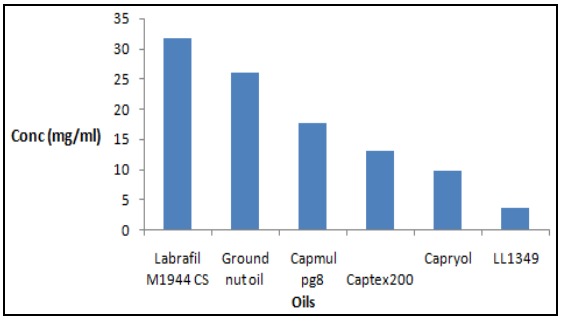

FIG. 5: SOLUBILITY OF OLMESARTAN IN VARIOUS OILS

Solubility of Olmesartan Medoxomil in Various Surfactants:

TABLE 3: SOLUBILITY OF OLMESARTAN MEDOXOMIL IN DIFFERENT SURFACTANTS

Surfactants	Concentration (mg/ml)
Span 80	19.26
Tween 80	28.35
Labrasol	22.56
Cremophore Rh	15.30

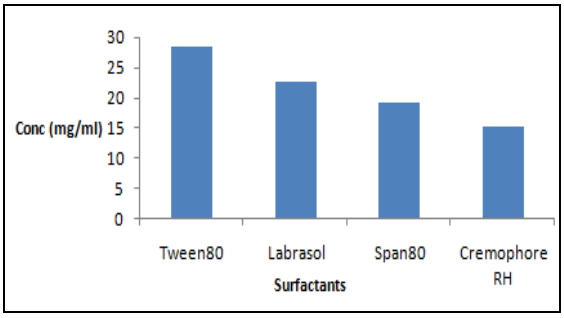

FIG. 6: SOLUBILITY OF OLMESARTAN IN VARIOUS SURFACTANTS

Solubility of Olmesartan Medoxomil in Various Co - Surfactants:

TABLE 4: SOLUBILITY OF OLMESARTAN MEDOXOMIL IN DIFFERENT CO-SURFACTANTS

Co -surfactant	Concentration (mg/ml)
Propylene glycol	14.135
Transcutol HP	15.498
Poly ethylene glycol 400	26.575

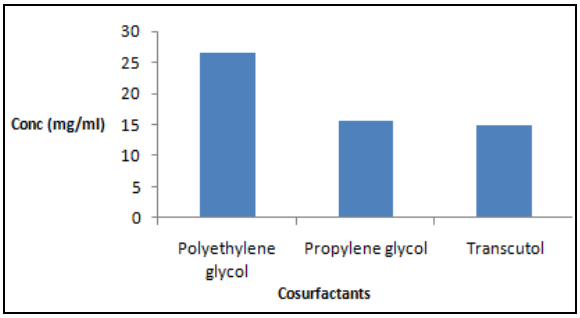

FIG. 7: SOLUBILITY OF OLMESARTAN IN VARIOUS CO- SURFACTANTS

Among the various vehicles / Excipients tested, maximum solubility of Olmesartan was observed in Labrafil M 1944 CS selected as the oily phase for formulating the SNEDDS system. Among the surfactants screened Tween 80 possess fine solubilisation and from co-surfactants Screened PEG400 and Propylene glycol were selected as the co-surfactant mixture for the preparation of SNEDDS.

Pseudo - Ternary Phase Diagrams: [3, 4] Pseudo - ternary Phase Diagrams are constructed to identify the nano emulsion regions and to identify suitable composition of oil, surfactant and co-surfactant for formulation of SNEDDS. From Pseudo - ternary phase diagrams it has been found that the systems consisting of Labrafil M 1944 CS was an oily phase, Tween 80 as the surfactant and Poly ethylene glycol 400 and Propylene glycol (PG) as co-surfactant showed good nano emulsifying

property though drug has been shown more solubility in systems containing Labrafil M 1944 CS as oil, Tween 80 as surfactant and Poly ethylene glycol 400 as co surfactant based on solubility studies.

For S_{mix} 4:1 ratio formulation LMTPEG41 showed Clear an bluish tinge Emulsion (BTE) for Oil: S_{mix} 1:9, 2:8; formulation LMTPEG41 showed slight turbid emulsion for Oil: S_{mix} 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1.

For S_{mix} 3:1 ratio formulation LMTPEG31 showed Clear Emulsion for Oil: S_{mix} 1:9 and slight turbid for remaining ratios.

For S_{mix} 1:4 ratio formulations LMTPEG14 showed slight turbid for all ratios of Oil: S_{mix}.

For S_{mix} 3:1 ratio formulations LMTPG31 showed Clear Emulsion for Oil: S_{mix} 1:9 and slight turbid for remaining ratios.

It was also found that for systems consisting of Labrafil M 1944 CS, Tween 80, Poly ethylene glycol400 an Propylene glycol by increasing co-surfactant proportion in S_{mix} systems had been shown decreasing property of forming nano emulsion. From this observation it is also clear that Surfactant is playing role to form nano emulsion in a proper range

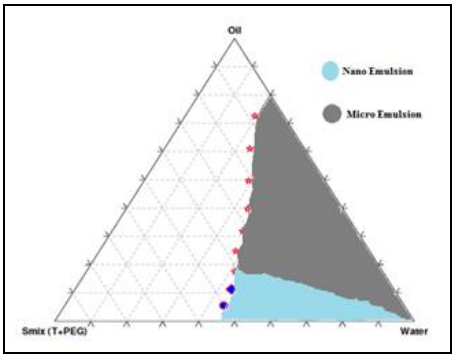

FIG. 8: PHASE DIAGRAM OF LMTPEG31

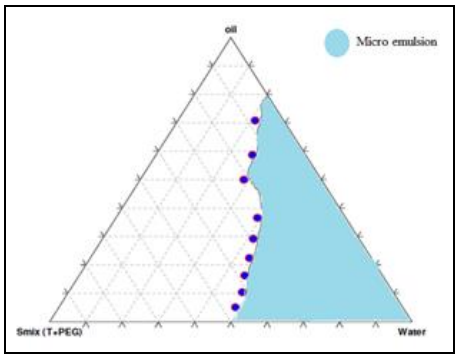

FIG. 9: PHASE DIAGRAM OF LMTPEG14

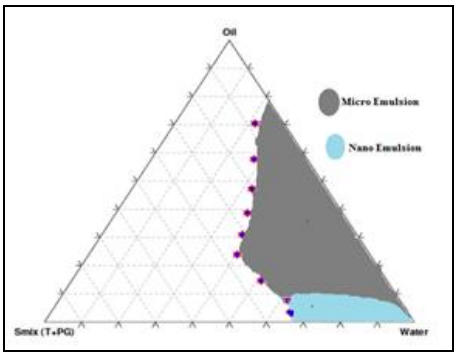

FIG. 10: PHASE DIAGRAM OF LMTPEG41

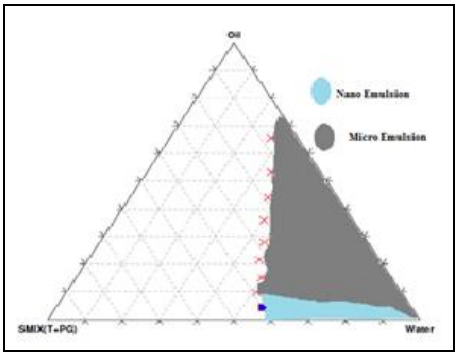

FIG. 11: PHASE DIAGRAM OF LMTPG31

TABLE 5: INTERPRETATION OF FUNCTIONAL GROUPS

Functional Group	Olmesartan (cm^{-1})	Olmesartan + Labrafil M 1944 CS (cm^{-1})	Olmesartan + Tween 80 (cm^{-1})	Olmesartan + PEG400 (cm^{-1})
Aromatic 3º amine N-H Stretch	2965.1	2925.2	2916.3	2876.8
C – N (Aromatic 3º amine C-N stretch)	1299.5	1244.7	1252.01	1299.6
Aromatic 2º amine N-H Stretch	3289.9	3467.7	3454.6	3382.7
C – N (Aromatic 2º amine C-N stretch)	1390.5	1377.8	1353.1	1352.6
C=O Stretch	1706.6	1742.6	1734.7	1704.5
C-O-C	1134.8	1167.9	1025.4	1117.5

FT-IR Spectroscopy: [13, 14]

Drug -Excipient Compatibility Studies: Fourier transformed infrared (FTIR) spectra was taken by using the KBr disk method. The scanning range was 400 to 4000 cm^{-1} and resolution was 1 cm^{-1}. The major peaks in recorded spectrum were as compared with standard spectrum given below.

So it can be accomplished that the spectra of pure drug Olmesartan and the combination of drug with additives, it was observed that all the characteristic peaks of Olmesartan were present in combination spectra, thus indicating compatibility of drug and excipients.

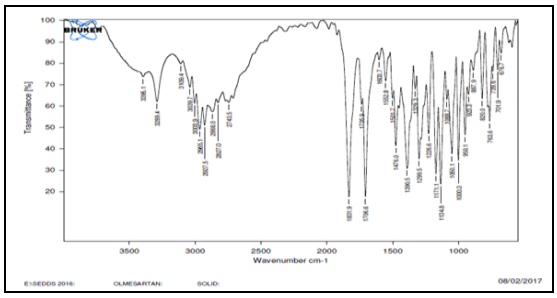

FIG. 12: FT-IR SPECTRA OF PURE DRUG (OLMESARTAN MEDOXOMIL)

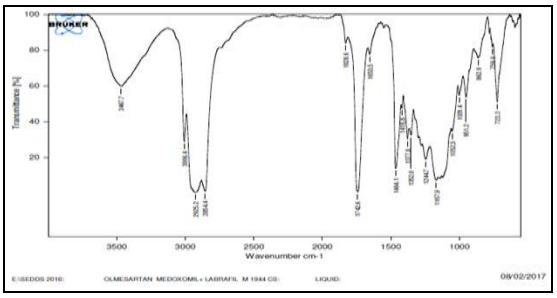

FIG. 13: FT-IR SPECTRA OF OLMESARTAN + LABRAFIL M1944

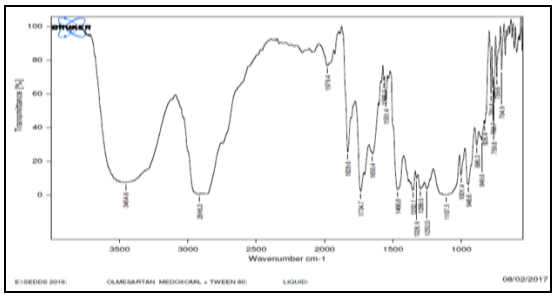

FIG. 14: FT-IR SPECTRA OF OLMESARTAN + TWEEN 80

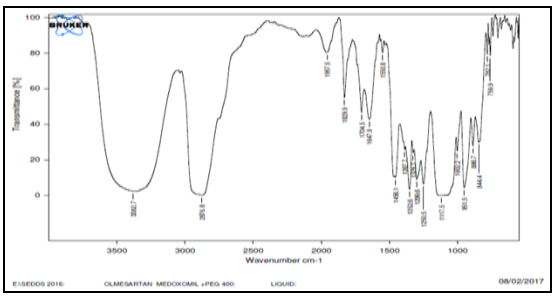

FIG. 15: FT-IR SPECTRA OF OLMESARTAN + PEG40

Self - Emulsification and Visual Evaluation: According to visual assessment formulations are grade for self-emulsification time. Self emulsifying Mixtures must disperse rapidly in aqueous medium on mild shaking. Self emulsification time that was determined for prepared SNEDDS given in **Table 6**. The prepared self -emulsifying formulations of Olmesartan were emulsified less than 1 min. The efficiency of all prepared emulsions was good.

TABLE 6: SELF EMULSIFICATION TIME (SECONDS)

Formulation name	Distilled water	0.1N HCl	Phosphate buffer pH 6.8
LMTPEG41-1	41.83±1.70	39.73±2.70	42.63±2.80
LMTPEG31-2	52.86±1.38	51.96±1.58	52.26±1.78
LMTPG41-2	42.33±2.93	41.23±2.53	40.33±2.43
LMTPEG41-4	52.66±1.22	51.76±1.42	53.56±1.12
LMTPG31-2	45.31±1.88	45.51±1.28	43.21±1.58

All values are expressed as Mean ± SD (n = 3)

Dispersibility Test: All the formulations have shown grade 1 emulsion when the test is performed in distill water, 0.1N HCl and buffer of pH 6.8.

TABLE 7: DISPERSIBILITY TEST RESULTS

Formulation name	Distilled water	0.1N HCl	Phosphate buffer pH 6.8
LMTPEG41-1	Grade 1	Grade 1	Grade 1
LMTPEG31-2	Grade 1	Grade 1	Grade 1
LMTPG41-2	Grade 1	Grade 1	Grade 1
LMTPEG41-4	Grade 1	Grade 1	Grade 1
LMTPG31-2	Grade 1	Grade 1	Grade 1

Phase Separation and Stability Study of Emulsions: Formulated SNEDDS preparations are viewed for phase separation and precipitation of drug. At time intervals of 2, 4, 6, 8, 12, 24 h periods of time and all formulations showed neither precipitation nor phase separation of the drug.

TABLE 8: PHASE SEPARATION AND PRECIPITATION OF THE DRUG (n = 3)

Formulation name	Phase separation	Precipitation
LMTPEG41-1	No	No
LMTPEG31-2	No	No
LMTPG41-2	No	No
LMTPEG41-4	No	No
LMTPG31-2	No	No

Effect of Dilution: Formulated SNEDDS Preparations are diluted with excess of distill Water, 0.1N HCl and buffer of pH 6.8 and the Diluted samples are stored for 24 h and observe visually for precipitation (or) phase separation of drug. No precipitation (or) phase separation is found which indicates the formulations are stable.

TABLE 9: EFFECT OF DILUTION (n = 3)

Formulation name	Distilled water	0.1N HCl	Phosphate buffer pH 6.8
LMTPEG41-1	*P	*P	*P
LMTPEG31-2	*P	*P	*P
LMTPG41-2	*P	*P	*P
LMTPEG41-4	*P	*P	*P
LMTPG31-2	*P	*P	*P

*P –Indicates all formulations are Robust to dilution

Percentage Transmittance: Each of the Diluted sample were observed for % Transmittance at 257 nm. Results are in **Table 10**. All formulations showed %transmittance more than 95% indicating that clear emulsion.

TABLE 10: PERCENTAGE TRANSMITTANCE (% TRANSMITTANCE)

Formulation name	Distilled water	0.1N HCl	Phosphate buffer pH 6.8
LMTPEG41-1	97.53±0.53	98.064±032	97.87±0.242
LMTPEG31-2	98.352±0.815	97.152±0.125	98.62±0.312
LMTPG41-2	98.131±0.324	97±0.269	97.12±0.281
LMTPEG41-4	96.612±0.412	97.152±0.511	98.685±0.215
LMTPG31-2	95.681±0.319	96.381±0.915	95.995±0.265

All values are expressed as Mean ± SD (n = 3)

Drug Loading Efficiency: [14] 50 mg of SNEDDS formulations was diluted with 100mL Methanol. Resultant solutions are analyzed UV-Spectro-photometrically by suitable dilution. Absorbance of each solution is measured at 257 nm. Results are in **Table 11**. It was found that all the formulations have drug loading efficiency is more than 90%.

TABLE 11: DRUG LOADING EFFICIENCY OF FORMULATIONS

Formulation name	Drug loading Efficiency
LMTPEG41-1	98.152 ± 0.312
LMTPEG31-2	96.859 ± 0.34
LMTPG41-2	97.649 ± 0.251
LMTPEG41-4	89.251 ± 0.412
LMTPG31-2	86.812 ± 0.118

All values are expressed as Mean ± SD (n = 3)

Thermodynamic Stability Studies: Thermodynamic stability study is intended to identify metastable formulations. The prepared self - emulsifying formulations are undergoing Centrifugation study and Freeze thaw cycle. The emulsions stable during centrifugation at 3,500 rpm and alternative temperature cycles of -20 ºC and +25 ºC.

TABLE 12: THERMODYNAMIC STABILITY STUDIES

Formulation name	Centrifugation (3,500 rpm for 30 min)	Freeze thaw cycle (-20 ºC and +25 ºC)
LMTPEG41-1	*P	*P
LMTPEG31-2	*P	*P
LMTPG41-2	*P	*P
LMTPEG41-4	*P	*P
LMTPG31-2	*P	*P

*P – Indicates all formulations are Stable

***In - vitro* Drug Release Study:** [15, 16] After performing the drug release study up to 90 min in 0.1N HCl (1.2 pH) for pure drug showed the percent drug release of pure drug 36.25% and the LMTPEG4:1 (1) showed 88.596% drug release and LMTPG4:1 (2) showed 84.896% drug release and LMTPEG3:1 (1) showed 84.171 Percent drug release.

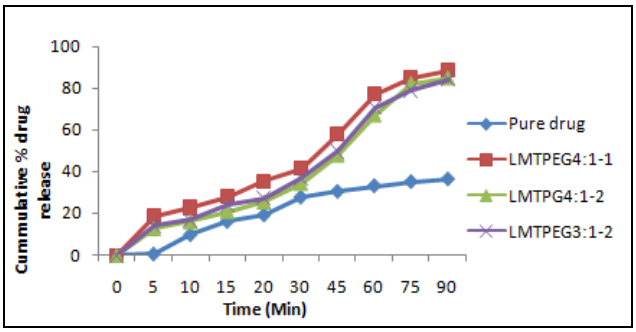

FIG. 16: CUMULATIVE % RELEASE OF PURE DRUG AND FORMULATIONS IN 0.1N HCl OF pH 1.2

Droplet Size Measurement and Zeta Potential Determination:

TABLE 13: PARTICLE SIZE AND ZETA POTENTIAL OF SNEDDS FORMULATIONS

Formulation name	Size of emulsion droplets (d.nm)	Region	Zeta potential (mV)	PDI
LMTPEG41-1	40.19	Nano	-14.6	0.403
LMTPEG31-2	113.7	Micro	-5.83	0.518
LMTPG41-2	125.7	Micro	-9.62	0.408
LMTPEG41-4	18.98	Nano	-7.09	0.391
LMTPG31-2	63.23	Nano	-3.84	0.542

***In-vitro* Characterization of Solid-SNEDDS of Olmesartan:** [17, 18] From the above all liquid SNEDDS Preparations LMTPEG41-1 is selected as optimized formulation for solid conversion because it posses good *in-vitro* properties and better drug release and droplet size distribution.

Flow properties and Re-constitution properties of S-SNEDDS: Flow properties such as Angle of Repose, Bulk density, Tapped density, Compressibility Index and Hausner's Ratio [17] are determined and it was found that Prepared S-SNEDDS showed "Good" flow properties. Results are given in **Table 14** and **15**.

TABLE 14: FLOW PROPERTIES OF S-SNEDDS OF OLMESARTAN

Flow Properties	Results
Angle of repose	28.275 ± 1.021
Bulk density (g/mL)	0.369 ± 0.014
Tapped density (g/mL)	0.42 ± 0.016
Compressibility index (%)	9.86 ± 0.039
Hausner's ratio	1.139 ± 0.008

All values are expressed as Mean ± SD (n = 3)

Reconstitution Properties of S-SNEDDS:

TABLE 15: RE-CONSTITUTION PROPERTIES OF S-SNEDDS

Formulation name	Drug Content	Effect of dilution	Particle size (d.nm)	Zeta potential (mV)
S-SNEDDS	95.162 ± 1.36%	pass	58.5	-15.3

***In - vitro* Drug Release Study from S-SNEDDS:** [18] After performing *in-vitro* drug release study for 90 min in 0.1 N HCl solid SNEDDS showed the % drug release of 86.89%, whereas for pure drug Cumulative percent of drug release was found to be 36.25%. From this it was clear that formulated S-SNEDDS increased solubility of poorly aqueous soluble drug Olmesartan thereby increased its percentage drug release. Results are given in **Fig. 17**.

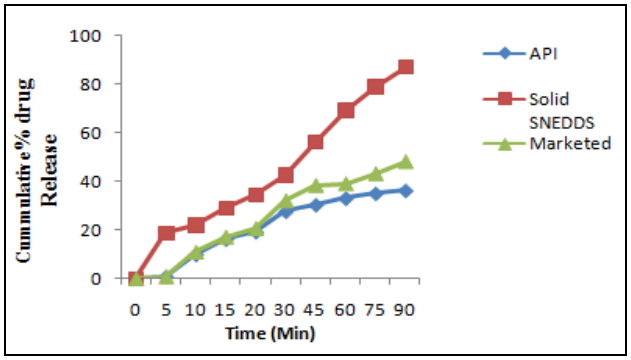

FIG. 17: *IN – VITRO* DISSOLUTION PROFILE OF PURE DRUG, S-SNEDDS AND MARKETED FORMULATION

CONCLUSION: Self - nanoemulsifying drug delivery system of poorly soluble drug Omlesartan medoxomil were prepared with Labrafil M 1944 CS (oil), Tween 80 (surfactant), Polyethylene glycol 400, Propylene glycol (co-surfactants). Prepared formulations were evaluated for different parameters like self emulsification time, phase separation studies, robustness to dilution, percent transmittance, droplet size and zeta potential and Thermodynamic stability studies. All the formulations are showed satisfactory results for those parameters. The Olmesartan loaded Preparations were subjected to *in-vitro* dissolution studies and results showed that all three formulations showed good release LMTPEG4:1(1) showed 88.596% drug release and LMTPG4:1(2) showed 84.896% drug release and LMTPEG3:1(1) showed 84.171%. They showed considerable increase in drug release compared to the plain drug (36.25%).

One formulation (LMTPEG4:1-1) is selected for the conversion into solid by using solid adsorption technique. NeusilinUS2 as solid carrier based on the Particle size and zeta potential. The prepared Solid-SNEDDS are characterized for the flow properties like Angle of repose, Carr's index and Hausner's ratio and that formulation showed good flow properties. Then the drug loaded S-SNEDDS were fills in capsules and subjected to In-vitro dissolution and it show good drug release compared to plain drug.

From the entire study it was concluded that an increase in both Solubility and Dissolution of Olmesartan by S-SNEDDS as compared to Dissolution rate of plain drug.

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CONFLICT OF INTEREST: Nil

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