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FORMULATION AND EVALUATION OF SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM FOR IMPROVED ORAL DELIVERY OF OLMESARTAN MEDOXOMIL

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Keywords:

Olmesartan Medoxomil, solid self-micro emulsifying drug delivery system, adsorption, droplet size, dissolution, absorption

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ABSTRACT: The present work aimed at formulating a solid self micro emulsifying drug delivery system (solid-SMEDDS) for Olmesartan Medoxomil with the objective of improving the aqueous solubility, dissolution and oral delivery of the drug. Liquid SMEDDS of the drug were formulated using Capmul MCM as the oil phase, Tween 80 and Phenoxide HCO-40 as the combined surfactants after screening various vehicles. The prepared systems were characterized for various physicochemical characteristics. Ternary phase diagrams were plotted to identify the area of micro emulsification. The optimized liquid SMEDDS was transformed into a free flowing powder using Neusilin US2 as the adsorbent. The physical state of the drug in solid self micro emulsifying powder was revealed by Differential Scanning Calorimetric and X– ray powder diffraction studies which indicated the presence of the drug in the dissolved form in the lipid excipients. These findings were supported by scanning electron microscopy studies which did not show the evidence of precipitation of the drug on the surface of the carrier. Moreover the droplet size of the micro emulsion formed from self microemulsifying powder remained same as that from the liquid SMEDDS. The dissolution of the drug was enhanced significantly from the SMEDDS formulation as compared to pure drug. Similarly the drug exhibited enhanced absorption from the SMEDDS formulation through rat intestinal segment compared to its suspension. Thus it can be concluded that a lipid based drug delivery system in the solid form can be successfully developed with the potential of enhancing the solubility, dissolution and oral absorption of the drug.

INTRODUCTION: Olmesartan Medoxomil (OLM) is an angiotensin II receptor blocker used to treat high blood pressure.[1]OLM is an ester-type prodrug that is deesterified during and/ or after its absorption in the gastrointestinal tract to produce an active compound, Olmesartan.

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However, the absorption behavior of the prodrug remains unclear. The oral bioavailability of OLM is as low as 26% in humans due to several factors, including low aqueous solubility, efflux by P-glycoprotein (P-gp), and unfavorable breakage of the ester drug in the gastrointestinal fluids to a poorly permeable parent molecule.[2-5] Lipid based formulations represents a unique solution to delivery of poorly soluble compounds. A lipid dosage form typically consists of one or more drugs dissolved in a blend of lipophilic excipients such as triglycerides, partial glycerides, surfactants or co-surfactants.[6]Among the lipid-based system, the

self-micro emulsifying drug delivery system (SMEDDS) is a promising technology to improve the rate and extent of absorption of poorly water soluble drugs. Self-micro emulsifying drug delivery system (SMEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including cosolvents, which emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastro-intestinal tract. Hydrophobic drugs can often be dissolved in SMEDDS allowing them to be encapsulated as unit dosage forms for peroral administration.[7]When such a system is released in the lumen of the gastrointestinal tract, it disperses to form a fine emulsion (micro/nano) with the aid of GI fluid.

This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first pass effect.[8]SMEDDS formulations are viscous liquids and thus marketed usually in the form of soft gelatin capsules, which have some drawbacks in the manufacturing process such as difficulty in process control, leakage of the encapsulated components, high production cost, and lower stability.[9]To address these problems, several attempts have been made to transform liquid SMEDDS into solid dosage forms using solid carriers or adsorbents. The solid forms of SMEDDS are able to offer the advantages of SMEDDS in combination with those of solid dosage forms such as production reproducibility and improved stability when they would lead to the formation of fine or micro emulsion at a similar rate exhibited by liquid SMEDDS.[10]

The present investigation was aimed at developing SMEDDS for improving the solubility, dissolution and oral absorption of OLM.

MATERIALS AND METHODS:

Materials:

Olmesartan Medoxomil was obtained as a generous gift from Cipla Pharmaceuticals Pvt. Ltd., Mumbai, India. Captex 300, Captex 355, Captex 500, Acconon CC-6 and Capmul MCM were kindly supplied by Abitec Corporation, Janesville, USA while LabrafilM 1944, Lauroglycol, Labrafac Lipophile WL 1349 and Labrasol were gifted by Gattefosse Ltd., Mumbai, India. Neusilin US2 was supplied by Gangwal Chemicals, Mumbai, India. Phenoxide HCO-40 was received as a gift sample from Phoenix Chemical Inc., Somerville, New Jersey. Tween 80, Span 80, Span 20, PEG 400 and Propylene glycol were purchased from Merck (Mumbai, India). All the excipients and reagents were of analytical grade and double distilled water was freshly prepared whenever required throughout the study.

Methods:

Solubility Studies:

Solubility studies were carried by placing an excess amount of OLMin a screw capped vials containing 2mL of vehicles (oils, surfactants and co-surfactants). The suspensions of vehicles were heated on a water bath at 40 °C to facilitate the solubilization using vortex mixer. The suspensions were then continuously agitated on a rotary shaker for 48h at ambient temperature. After reaching equilibrium the samples were centrifuged at 5000 rpm for 15min and the supernatant was taken, filtered through 0.45µm membrane filters. The filtrates were suitably diluted with methanol and analyzed spectrophotometrically for the dissolved drug at 257nm.Blank was prepared by dissolving respective vehicles in methanol with same dilution as for the samples. The experiment was performed in triplicate and results were represented as mean value (in milligram/mL) ± SD.

Construction of Pseudoternary Phase Diagrams:

The selected oil, surfactant, co-surfactant on the basis of solubility and preliminary screening studies were used to develop pseudoternary phase diagrams using water titration method.[11]The various surfactant/co-surfactant (S_{mix}) ratios were prepared using different proportions of surfactant and co-surfactant (1:1, 2:1 and 1:2) for formation of transparent clear solution. A series of oil/S_{mix}mixtures were prepared at all nine combinations (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) and titrated with water to identify the microemulsion region.

The total water consumed was noted in terms of w/w and during titration of oil-S_{mix}ratio, observations were made for phase clarity. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occur were derived from the weight measurements. These values were used to

determine the boundaries of the microemulsion region corresponding to the selected value of oil and S_{mix}ratio. Phase diagrams were constructed using CHEMIX school software, version 3.6.

Preparation of Liquid SEDDS:

A series of SMEDDS formulations were prepared with varying ratios of oil (20-40 %), surfactant (30-70 %) and co-surfactant (10-50 %). A single dose of OLM (20 mg) was incorporated in all formulations. The total weight of the formulations was kept at 240 mg. The formulations were prepared by dissolving the drug in oil followed by addition of surfactant and co surfactant in glass vials. The resulting mixtures were stirred continuously by vortex mixing followed by sonication for few minutes to obtain a homogenous isotropic mixture. The SMEDDS formulations were stored at ambient temperatures until further use.

Characterization of SMEDDS:

Visual Assessment of Self- Emulsification:

A visual test to assess the self-micro emulsification properties reported by Craig et al. was modified and adopted in the present study. In this method, a unit dose of the formulation was introduced into 250mL of water in a glass beaker that was maintained at 37 ± 0.5ºC and the contents mixed gently using a magnetic stirrer. The tendency to emulsify spontaneously and the time taken for the emulsion formation were assessed visually. All the trials were carried out in triplicate with similar observations being made between repeats.

Effect of pH and Robustness to Dilution:

Formulations were subjected to 50, 100, 250 and 1000 fold dilution with distilled water, pH 1.2 and pH 6.8 buffer. The resultant diluted emulsions were monitored for any physical changes such as (coalescence of droplets, precipitation or phase separation) after 24 h storage.[12]

% Transmittance, Droplet size and PDI:

The SMEDDS were reconstituted with distilled water and the resulting micro emulsions were observed visually for any turbidity. Thereafter its % transmittance was measured at 650 nm using UV-visible spectrophotometer (Jasco V-630, Japan) against distilled water as the blank. The studies were conducted after 100 times dilution.

The mean droplet size (SMD) and polydispersity index (PDI) of the formulations were determined by photon correlation spectroscopy using nanosizer (Nanophox NX0088, SympatecGermany). Each formulation was diluted with filtered (0.45 µm, Millipore) double distilled water before analysis. Size analysis was carried at 25 °C with an angle of detection of 90°.The globule size distribution was expressed in terms of polydispersity index, which is a measure of the width of the globule size distribution. It is defined as:

$$\text{Polydispersity Index}=\frac{X_{90}-X_{10}}{X_{50}}$$

where X_{90}, X_{10} and X_{50} are standard percentage readings from the globule size estimation. X_{50} is the mean globule size. X_{10}, X_{50} and X_{90} are the size of the globules below 10%, 50% and 90% respectively of the sample lies

Cloud Point, Refractive Index, Zeta Potential, and Tharmodynamic Stability:

The cloud point measurement was carried out for the formulations as reported earlier.[13]The formulation was diluted up to 100 folds with distilled water and kept in a water bath which was maintained at a temperature of 25 °C with gradual increase of temperature at a rate of 5 °C/min and the corresponding cloud point temperatures were read at first sign of turbidity by visual observation. The isotropicity of the SMEDDS preconcentrate (undiluted) was determined by refractive index measurement. Refractive index was measured by an Abbe refractometer (Bausch and Lomb Optical Company, Rochester, NY).Zeta potential of the liquid SMEDDS formulations was measured on Zetasizer (ZS 90, Malvern Zetasizer, Malvern, UK) after diluting the SMEDDS formulation with 100mL double distilled water. The formulations were diluted 100 times with distilled water and subjected to different thermodynamic stability test to assess their physical stability as mentioned below. All samples were evaluated in terms of phase separation at the end of analysis.[14]

Heating-cooling cycle: six cycles between refrigeration temperature (2-8 ºC) and 45 ºC with storage at each temperature not less than 48 h were conducted.

Centrifugation test: The formulations were centrifuged at 3500 rpm for 15 min and the extent of phase separation was monitored.[19]

Transmission Electron Microscopy (TEM):
The morphology of the optimized self-micro emulsifying drug delivery system (SMEDDS) formulation was observed using transmission electron microscope (JEM-2100 F, M/s Jeol, Tokyo, Japan) with AMT image capture engine software. SMEDDS formulation was diluted with distilled water in 1:200 and mixed by gentle shaking. One drop of the diluted sample was deposited on a film coated copper grid, stained with one drop of phosphotungstic acid and allowed to dry before observation under the transmission microscope. The image was magnified and focused on a layer of photographic film.

Preparation of Solid–Self Micro emulsifying Drug Delivery System (solid-SMEDDS):
Solid-SMEDDS was prepared by mixing liquid SMEDDS containing OLM with Neusilin US2 in 1:2, 1:1, and 2:1 proportions. In brief liquid SMEDDS was added gradually over the carriers contained in a mortar. After each addition, mixture was mixed vigorously and homogenized to ensure uniform distribution of formulation. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use.

Micromeritic Properties of Solid- SMEDDS:
The bulk density, tapped density, Carr's Compressibility Index and Hausner's ratio were determined for the optimized solid-SMEDDS. The angle of repose of self- micro emulsifying powder was determined by funnel method.[15] Briefly the sample was poured through a funnel with its tip positioned at a fixed height (h) on a horizontal surface until apex of pile touches the tip of the funnel. The angle of repose was calculated using the formula $\tan \theta = h/r$ where r is radius of the pile of powder.

Morphological Analysis: The outer macroscopic structure of the solid self- micro emulsifying powder and that of pure drug was investigated by scanning electron microscopy (JEOL, JSM-6390 LV, Japan) at 15 keV accelerating voltage.

Differential Scanning Calorimetry (DSC):
The physical state of the OLM in solid-SMEDDS was characterized by DSC studies. The DSC thermograms of the OLM, physical mixture of the drug and the carrier, carrier and that of solid-SMEDDS were recorded using differential scanning calorimeter (Perkin Elmer, USA). The samples were heated in an open aluminum pan from 30 to 450 °C at a scanning rate of 10 °C/min under the stream of nitrogen.

Powder X-Ray Diffraction Studies:
X-ray powder scattering measurements of the OLM, physical mixture of OLM with carrier, carrier and that of solid self- microemulsifying powder were carried out with X-ray diffractometer (D8 Advance, Bruker AXS, Germany). The Powder X-ray diffraction patterns were recorded at room temperature using monochromatic CuKα-radiation (k=1.5406 Å) at 40 mA and at 45 kV over a range of 2 θ angles from 3° to 50° with an angular increment of .02° per second.

Emulsion Droplet Size:
The mean droplet size (SMD) and polydispersity index (PDI) of solid-SMEDDS was determined by photon correlation spectroscopy using nanosizer (Nanophox NX0088, Sympatec Germany). The formulation was diluted with filtered (0.45 μm, Millipore) double distilled water before analysis. Size analysis was carried at 25 °C with an angle of detection of 90°.

Drug Content Estimation:
Liquid SMEDDS and solid-SMEDDS containing OLM, each equivalent to 20 mg was dispersed in suitable quantity of methanol. The samples were mixed thoroughly to dissolve the drug in methanol, centrifuged at 3000 rpm for 15 min using 12C micro-centrifuge (Remi motors, Mumbai, India) to separate the undissolved excipients. The supernatant was suitably diluted and analyzed spectrophotometrically at 257 nm using Jasco UV-visible spectrophotometer. Similarly the dissolution profile of pure drug was also carried out.

***In-vitro* Absorption Studies:**
In-vitro absorption studies of pure drug, liquid SMEDDS and solid-SMEDDS were carried out through everted rat intestinal segment using an in-

house fabricated perfusion apparatus.[16] The apparatus consists of two cylindrical glass tubes; one joined to other via J-shaped tapering end. Both the tubes are held together by a glass joint on the upper end. On the lower ends of both tubes a bulge is given for proper mounting of tissue. After mounting the everted intestinal segment on the apparatus and setting it in the beaker; the inside of the glass tubes serve as the serosal compartment and the beaker serves as the mucosal compartment. For experimental purpose the rat was sacrificed humanely by cervical dislocation and the abdomen was opened by midline incision.

A 9 cm intestinal segment corresponding to duodenal region was carefully removed and transferred to a petri dish containing Kreb's medium (118.0 mMNaCl, 4.7 mMKCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$ $7H_2O$, 25.0 mM $NaHCO_3$, 1.2 mM KH_2PO_4 and 5.5 mM glucose). The intestinal segment was cleaned with the Kreb's solution and gently everted using a glass rod. A 6.0 cm everted segment was then mounted in the apparatus which was placed in a 600.0 mL beaker containing the drug suspended in 500 mL of pH 5.8 buffer solution. The total volume of the absorption compartment (tubes of perfusion apparatus) was 30mL of Kreb's solution.

This assembly (beaker and apparatus with tissue) was placed on a magnetic stirrer and a magnetic bead was allowed to rotate at 25 rpm in beaker and the temperature was maintained at 37 ± 0.5 °C with adequate aeration. The drug diffused from phosphate buffer pH 5.8 (mucosal side) to the Kreb's solution contained in the tubes (serosal side). The samples were collected at different time points (at every 30 min for 3.0 h) from the serosal compartment and analyzed for the drug content by UV spectrophotometer. Similarly the absorption studies were carried out for the optimized liquid SMEDDS and solid-SMEDDS.

All the experiments were performed in triplicate. The study protocol for *in vitro* absorption was approved by the Institutional Animal Ethics Committee (IAEC) of Department of Pharmaceutical Sciences, Nagpur and is in accordance with guidance of Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

Statistical Analysis:

All the results were expressed as mean with standard deviation (mean ± S.D). The dissolution data obtained was subjected to student unpaired t test with Instant Graph pad Prism software (version 4.00; Graph Pad Software, San Diego California) for comparison between two samples. The difference at $P<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION:

Solubility Studies:

The components in the formulation of SMEDDS were selected to have maximum solubility of OLM along with good miscibility with each other to produce an isotropic and stable system. The results of solubility of OLM in various vehicles/excipients screened are shown in the **Fig. 1** and **2**.

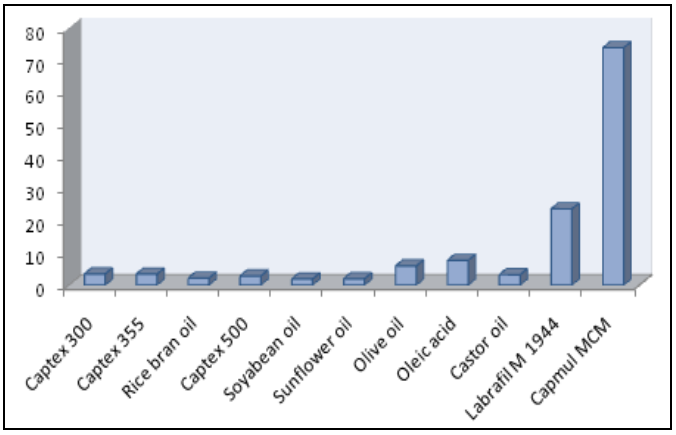

FIG.1: SOLUBILITY STUDIES OF OLMESARTAN MEDOXOMIL IN VARIOUS OILS. DATA EXPRESSED AS MEAN±SD, N=3

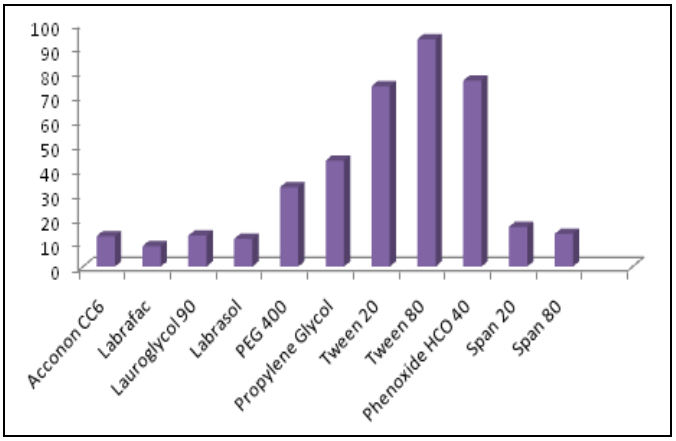

FIG.2: SOLUBILITY STUDIES OF OLMESARTAN MEDOXOMIL IN VARIOUS SURFACTANTS AND CO-SURFACTANTS. DATA EXPRESSED AS MEAN±SD, N=3

In the present study, amongst the various vehicles tested, highest solubility of OLM was observed in Capmul MCM followed by Labrafil M 1944. Capmul MCM is also reported to have good emulsifying properties and has GRAS (generally regarded as safe) status. Thus the same was chosen as the oily carrier phase for formulating the SMEDDS system. Amongst the surfactants screened Tween 80 and Phenoxide HCO-40 were found to possess good solubilization potential for OLM and were chosen as the surfactant mixture to formulate the SMEDDS.

Construction of Pseudoternary Phase Diagrams:
The construction of Pseudoternary phase diagrams makes it easy to find out the concentration range of components that results in self-emulsification. Although self-emulsification is a dynamic process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior.

There is a correlation between emulsification efficiency, formation of lamellar liquid crystalline dispersion phase, region of enhanced water solubilization and phase inversion region, after addition of water. To develop an optimum self-micro emulsifying formulation, self-micro emulsifying region in the phase diagram should be located.[17] Pseudoternary phase diagrams were constructed by using three different ratios of surfactant and co-surfactant combination and are presented in the **Fig. 3, 4** and **5**.

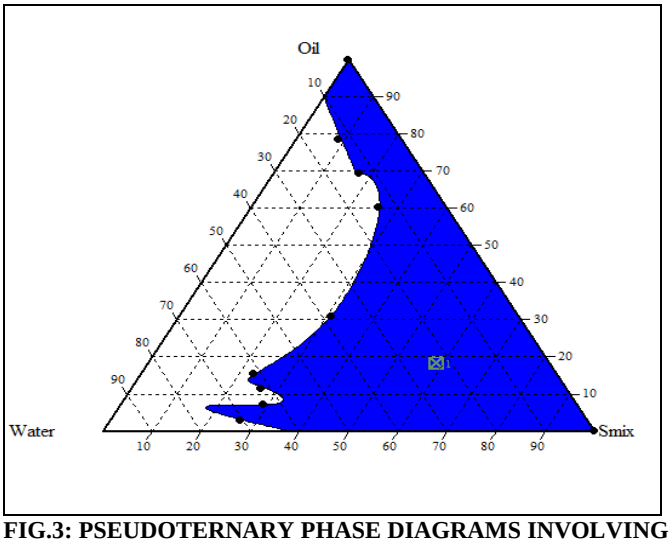

FIG.3: PSEUDOTERNARY PHASE DIAGRAMS INVOLVING CAPMUL MCM (OIL), TWEEN 80+PHENOXIDE HCO-40 (S_{mix}) AND WATER WITH RATIO OF SURFACTANT TO CO-SURFACTANT AS 1:1.

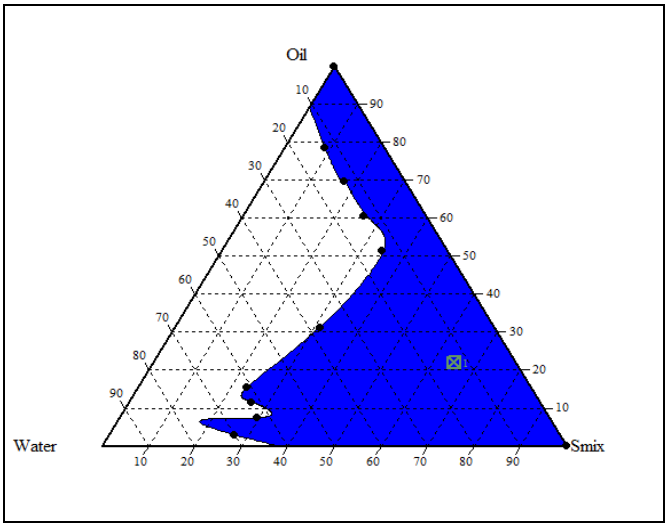

FIG.4: PSEUDOTERNARY PHASE DIAGRAMS INVOLVING CAPMUL MCM (OIL), TWEEN 80+PHENOXIDE HCO-40 (S_{mix}) AND WATER WITH RATIO OF SURFACTANT TO CO-SURFACTANT AS 2:1.

It can be deduced from figures that S_{mix} ratio 1:1 and 2:1havemoreemulsification area as compared to S_{mix} ratio 1:2. Moreover the S_{mix} ratio 1:1 and 2:1have almost the same emulsification area and hence for the formulation of SMEDDS the ratio of surfactant mixture was kept at 1:1, 2:1 and higher to arrive at the optimum concentration of surfactant and co-surfactant.

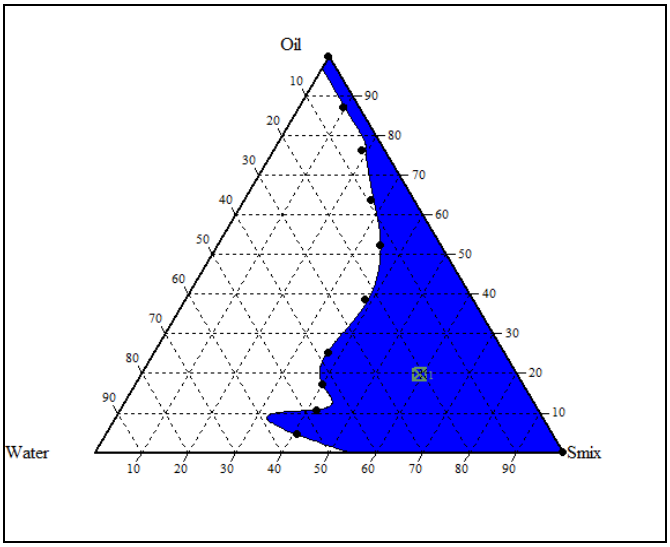

FIG.5: PSEUDOTERNARY PHASE DIAGRAMS INVOLVING CAPMUL MCM (OIL), TWEEN 80+PHENOXIDE HCO-40 (S_{mix}) AND WATER WITH RATIO OF SURFACTANT TO CO-SURFACTANT AS 1:2.

Preparation of Liquid SMEDDS:
Thirteen batches of liquid SMEDDS were prepared as per the composition depicted in **Table 1** which was then characterized for various parameters as shown in the same table.

TABLE 1: FORMULATION AND CHARACTERIZATION OF SMEDDS

BATCH	X	Y	Z	SET*	% TM*	AVG.SIZE	PDI
F1	20	80	0	43 ± 2.64	94.2 ± 1.45	121.88	0.323
F2	20	70	10	32 ± 1.5	99.1 ± 0.25	12.85	0.304
F3	20	60	20	35 ± 1	99.2 ± 0.81	16.06	0.330
F4	20	50	30	35 ± 2.5	99.1 ± 0.73	10.45	0.378
F5	20	40	40	34 ± 1.5	99.4 ± 0.47	15.92	0.298
F6	30	70	0	57 ± 3.0	89.5 ± 0.75	209.65	0.257
F7	30	60	10	57 ± 2.5	88.5 ± 1.15	173.23	0.274
F8	30	50	20	44 ± 2.0	88.6 ± 1.0	188.2	0.296
F9	30	40	30	56 ± 2.0	92.3 ± 1.80	121.8	0.332
F10	40	60	0	137 ± 3.0	82.1 ± 1.80	243.31	0.238
F11	40	50	10	124 ± 2	89.4 ± 0.95	202.21	0.363
F12	40	40	20	134 ± 2	84.4 ± 0.95	229.65	0.241
F13	40	30	30	125 ± 5	85.7 ± 1.05	194.28	0.297

X: % Oil, Y: % Surfactant, Z: % Co-surfactant, SET: Self emulsification time in seconds, %TM: % Transmittance, PDI: Polydispersity index

*Data expressed as mean ± SD (n=3)

Characterization of SMEDDS:

Visual Assessment of Self- Emulsification:

The liquid SMEDDS formulations (F1-F13) were subjected to assessment of efficiency of self-emulsification visually. It is quite essential that the SMEDDS should disperse completely and quickly on being diluted under mild agitation. In the present investigations, the self- emulsification time of all the SMEDDS formulations containing 20% and 30% of the oil phase were found to be below 60 seconds indicating the rapidity of emulsion formations. However formulations containing 40% of the oil phase had self-emulsification time greater than 120 seconds suggesting increase in the oil content led to a decrease in emulsification ability.

Formulations containing 20 % of oil phase on constitution with distilled water formed clear, transparent emulsions which can be termed as Grade A emulsions. Formulations containing 30% of the oil phase on constitution with water were observed to form translucent emulsions which can be categorized as Grade B emulsions except for formulation F9 which on dilution with water formed a transparent microemulsion (Grade A emulsion). However formulations with 40% of the oil content formed turbid, whitish emulsions which can be termed as Grade C emulsions.

Effect of pH and Robustness to Dilution:

It is desirable with regards to SMEDDS formulations that they should have not only the ability to emulsify rapidly but also should be able to form stable emulsions at different dilutions. The formulations are expected to undergo gradual dilution in contact with the GI fluid and the process should not lead to precipitation of the drug. Hence robustness to dilution was monitored by diluting the SMEDDS 50, 100, 250 and 1000 times with distilled water and with pH 1.2 and pH 6.8 buffer. It was found that the liquid SMEDDS formulations remained stable at different dilutions indicating the possibility of uniform release of the drug after its oral administration. Even after 24h, neither precipitation of the drug nor any phase separation was observed when the SMEDDS were diluted up to 1000 times, showing the stability of the reconstituted emulsion.

% Transmittance, Droplet Size and PDI:

The liquid SMEDDS formulations were characterized for % transmittance and droplet size analysis. It was revealed from the data that the % transmittance of all the formulations containing 20 % of the oil phases were greater than 95 % indicating a good clarity of the micro emulsions being formed which was confirmed by the resultant average droplet size of the formulations.

The droplet size of the emulsion is a crucial factor in self micro emulsification performance because it determines the rate and extent of drug release as well as absorbance.[18] Droplet size of formulations F2, F3, F4 and F5 at 100 times dilution was found to be below 20 nm while that of formulation F1 was below 125 nm. Formulations containing 30% of the oil phase formed translucent emulsions on being diluted with water with % transmittance

values less than 90 % except for formulation F9 which formed a transparent micro emulsion with % transmittance greater than 90 %. The average droplet size of formulations with 40% of the oil phase was determined to be below 250 nm. The PDI of most of the formulations was found to be < 0.3 indicating homogenous distribution of the oil globules.

Cloud Point, Refractive Index, Zeta Potential and Thermodynamic Stability:

The physicochemical parameters like cloud point, refractive index, zeta potential and thermodynamic stability were determined for formulations F1, F2, F3, F4 , F5 and F9having droplet size in the micro emulsion region. The results have been depicted in **Table 2.**

TABLE 2: PHYSICOCHEMICAL CHARACTERIZATION OF SMEDDS

Formulation	Cloud point(ºC)	Refractive index	Zeta potential (mv)	Thermodynamic stability
F1	78 ± 2.22	1.3405 ± 2.2	- 10.42	Stable
F2	80 ± 3.75	1.3304 ± 2.1	- 9.41	Stable
F3	79 ± 3.1	1.3303 ± 3.2	- 10.3	Stable
F4	82 ± 2.41	1.3305 ± 2.5	- 11.3	Stable
F5	78 ± 2.2	1.3303 ± 1.1	- 11.3	Stable
F9	82 ± 2.1	1.3502 ± 2.1	- 10.12	Stable

The cloud point is a vital parameter in assessing the stability of the SMEDDS formulations. The cloud point is the temperature above which the clarity of the formulation turns to cloudiness. This happens due to phase separation and precipitation of the drug from the micro emulsions formed from the SMEDDS which in turn will obviously hamper the drug release. To avoid this phenomenon the cloud point for SMEDDS should be above body temperature (37ºC). In the present case the cloud point temperatures of formulations F1, F2, F3, F4, F5 and F9 determined were in the range of 78-82 ºC. This infers not only good thermal stability of all the tested formulations but also gives an indication of unhindered drug release.

Zeta potential of the self - emulsifying formulations after dilution with water was determined by zeta sizer. It was revealed that the zeta potential values of formulation F1, F2, F3, F4, F5 and F9 were negative due to the presence of fatty acid and glycol present in oil and surfactant. The refractive indices of the undiluted SMEDDS were found to range between 1.3303-1.3502 indicating the transparent features of the formulations. The objective of thermodynamic stability study was to evaluate the phase separation and effect of temperature variations on developed SMEDDS in order to exclude the possibility of metastable formulations. The study revealed excellent stability of various formulations of OLM with no signs of phase separation or precipitation at various stress conditions studied.

Considering the physicochemical characteristics of the SMEDDS formulations and the droplet sizes of the micro emulsions obtained in particular, the optimized liquid SMEDDS formulation was considered as F5 with a droplet size of 15.92 nm and PDI of 0.293, a feature which was considered desirable with regards to homogeneity of droplet size distribution as compared to formulation F2, F3 and F4 which produced microemulsions with droplet sizes less than 20 nm but with higher PDI values.

Transmission Electron Microscopy (TEM):

Fig. 6 portrays the electron microscopic image depicting the morphology of the reconstituted optimized formulation, F5.

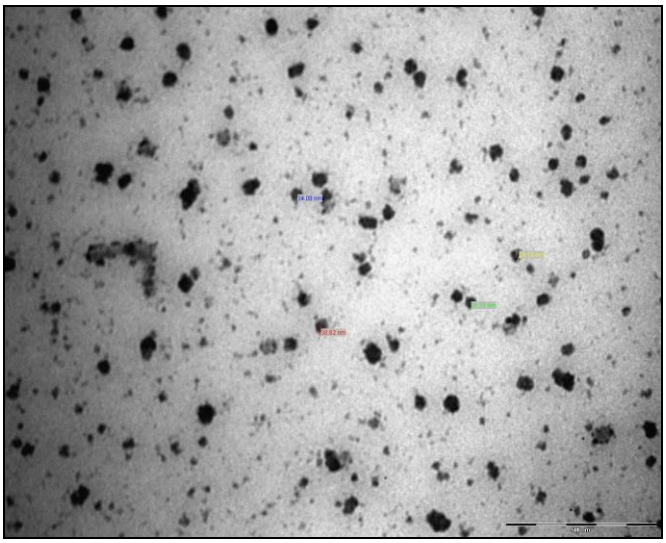

FIG. 6: TEM IMAGE OF OPTIMIZED RECONSTITUTED LIQUID SMEDDS F5

Preparation of Solid Self-Microemulsifying Drug Delivery System (solid-SMEDDS):

Transforming liquid SMEDDS of a poorly water soluble drug into solid enables the development of capsules or tablets. In addition to providing the obvious benefit of a SMEDDS, a high content of liquid SMEDDS can be loaded onto variety of carriers which maintains good micromeritic properties and helps in production of solid dosage forms. Various options are available for transformation of liquid SMEDDS into solid like adsorption on to solid carriers, spray drying, freeze drying and other techniques. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender.

The resulting powder may then be filled directly into capsules or alternatively, mixed with suitable excipients before compression into tablets. The adsorption process was adopted in the present study for preparing solid-SMEDDS for which the carrier chosen was NeusilinUS2. Thus the liquid SMEDDS containing OLM were adsorbed onto NeusilinUS2 in 1:1, 1:2 and 2:1 proportions. Neusilin US2 is an ultra-light granular synthetic, amorphous form of magnesium alumina metasilicate, prepared by spray drying process. It has highly porous structure with large surface area and good oil adsorbing capacity. A1:1 proportion of Neusilin US2: liquid SMEDDS was sufficient to obtain a free flowing powder. The appearance of the powder was such that one would have difficulty to recognize that the powder contained an equal weight of oily liquid.

Micromeritic Properties of Solid-SMEDDS:

The micromeritic properties of solid-SMEDDS prepared with Neusilin US2 was determined to evaluate the flow properties of the powders. It was revealed that the bulk and tap densities of powders prepared with Neusilin US2 was found to be 0.4346±0.011and 0.4623±0.005respectively.

The solid-SMEDDS exhibited good flow characteristics with Carr's index value as 12.4 ± 1.2, Hausner's ratio as 1.13± 0.01 and angle of repose (θ) as 24.2± 2. Thus it can be inferred that the prepared solid-SMEDDS with the porous carrier have the ability to be processed into solid dosage form.

Morphological Analysis:

The scanning electron micrographs in **Fig. 7** revealed OLM as crystalline powder with irregular shaped crystals. The solid-SMEDDS prepared with Neusilin appeared as rough surfaced particles with no evidence of precipitation of the drug on the surfaces of the carriers indicating that the liquid SMEDDS was absorbed or coated inside the pores of Neusilin.

As is evident from the figure, all the globules were of uniform shape, with globule size less than 50 nm. The figure clearly illustrate that there are no signs of coalescence, indicating thereby the enhanced physical stability of the formulation.

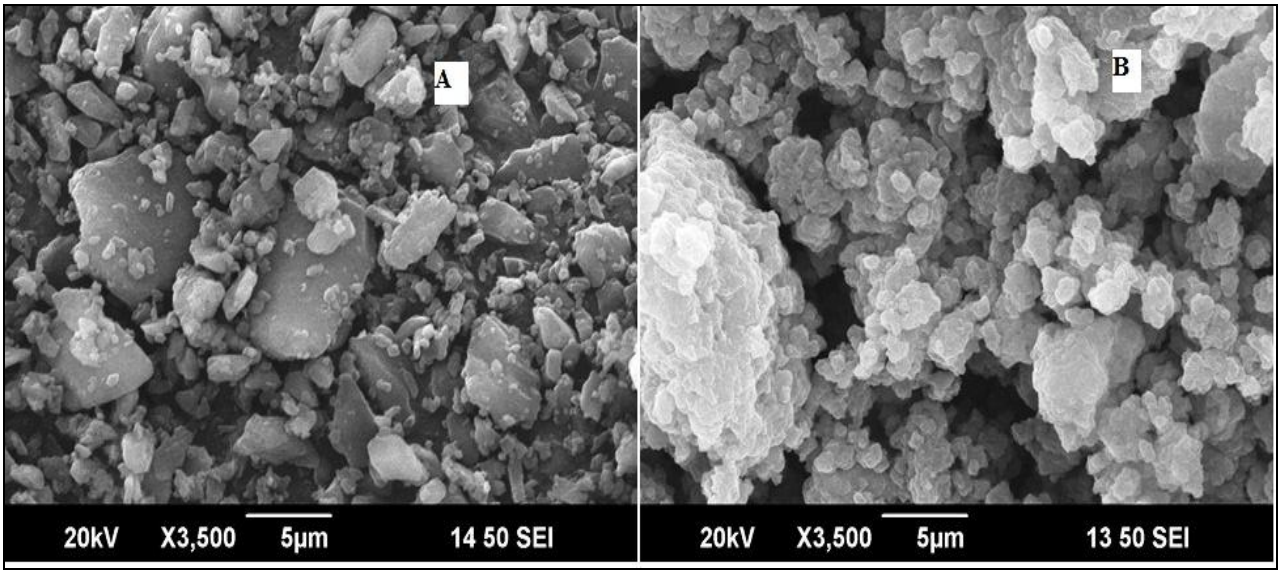

FIG.7: SCANNING ELECTRON MICROGRAPHS OF (A) PURE OLM AND (B) SOLID-SMEDDS

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the OLM, physical mixture of OLM and Neusilin, Neusilin and solid self- micro emulsifying powders are shown in **Fig.8**. The DSC thermogram of pure OLM exhibited sharp endothermic peak at 184.20 ºC, corresponding to OLM melting point and which infers presence of OLM in crystallineform. The physical mixture of OLM and Neusilin US2 showed endothermic peak of the drug but with reduced intensity. No prominent peaks were observed for Neusilin US2 over the entire range of temperature studied. However, no representative peak of OLM was observed for solid-SMEDDS signifying the capability of the self-emulsifying ingredients in maintaining the drug in dissolved state and/or inhibiting recrystallization of the drug.

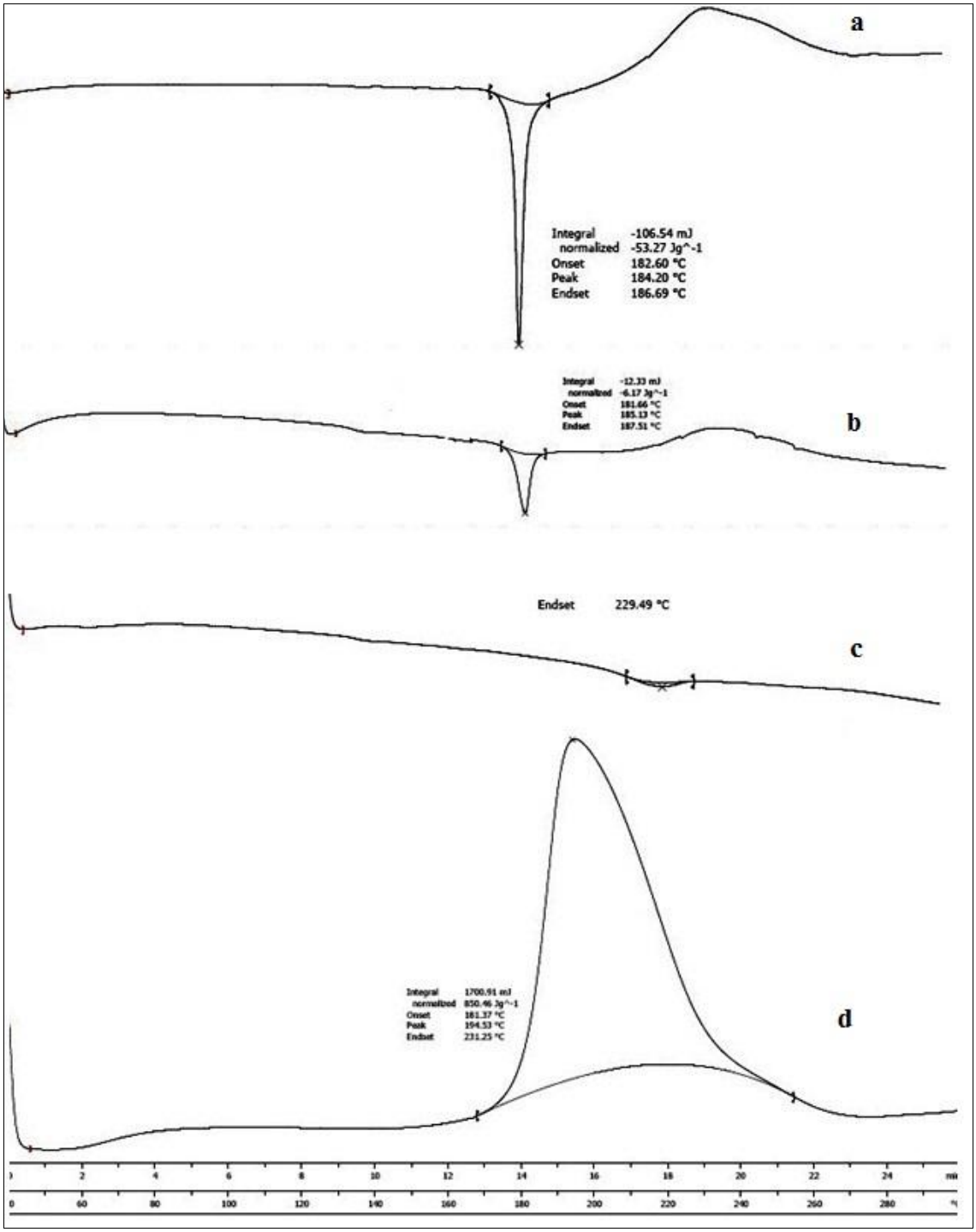

FIG. 8: DIFFERENTIAL SCANNING CALORIMETRIC THERMOGRAMS OF (a)OLMESARTAN MEDOXOMIL (b) PHYSICAL MIXTURE OF OLM AND NEUSILIN (c) NEUSILIN AND (d) SOLID-SMEDDS

X-Ray Powder Diffraction Studies:

X-ray diffraction studies have been most valuable in elucidation of phase behavior, arrangement and crystal order of molecules. The powder X-ray diffraction studies were carried out to assess the physical state of the drug in the prepared solid self - emulsifying formulations. Thus the X-ray diffraction pattern of OLM, physical mixture of OLM and Neusilin, Neusilin as well as that of solid-SMEDDS is shown in **Fig. 9**. The diffraction pattern of OLM (**Fig.** as of **9**) showed high intensity peaks at 2 theta values of 7.262, 9.181, 10.642, 11.656, 12.728, 14.508, 18.512, 20.624, 24.700, 27.551, 29.085 and 33.678 respectively.

Sharp intense peaks observed in the diffractograms indicate the presence of crystalline form of the drug. The peak intensity of the drug was found to be reduced in its physical mixture with the carrier, Neusilin.

The diffractograms of the carrier was characterized by diffuse spectra which is typical of amorphous material. The diffractograms of solid-SMEDDS prepared with Neusilin US2 was characterized by diffuse peak suggesting that the drug was present in solubilized state in the lipid excipients and or transformed from crystalline to amorphous form.

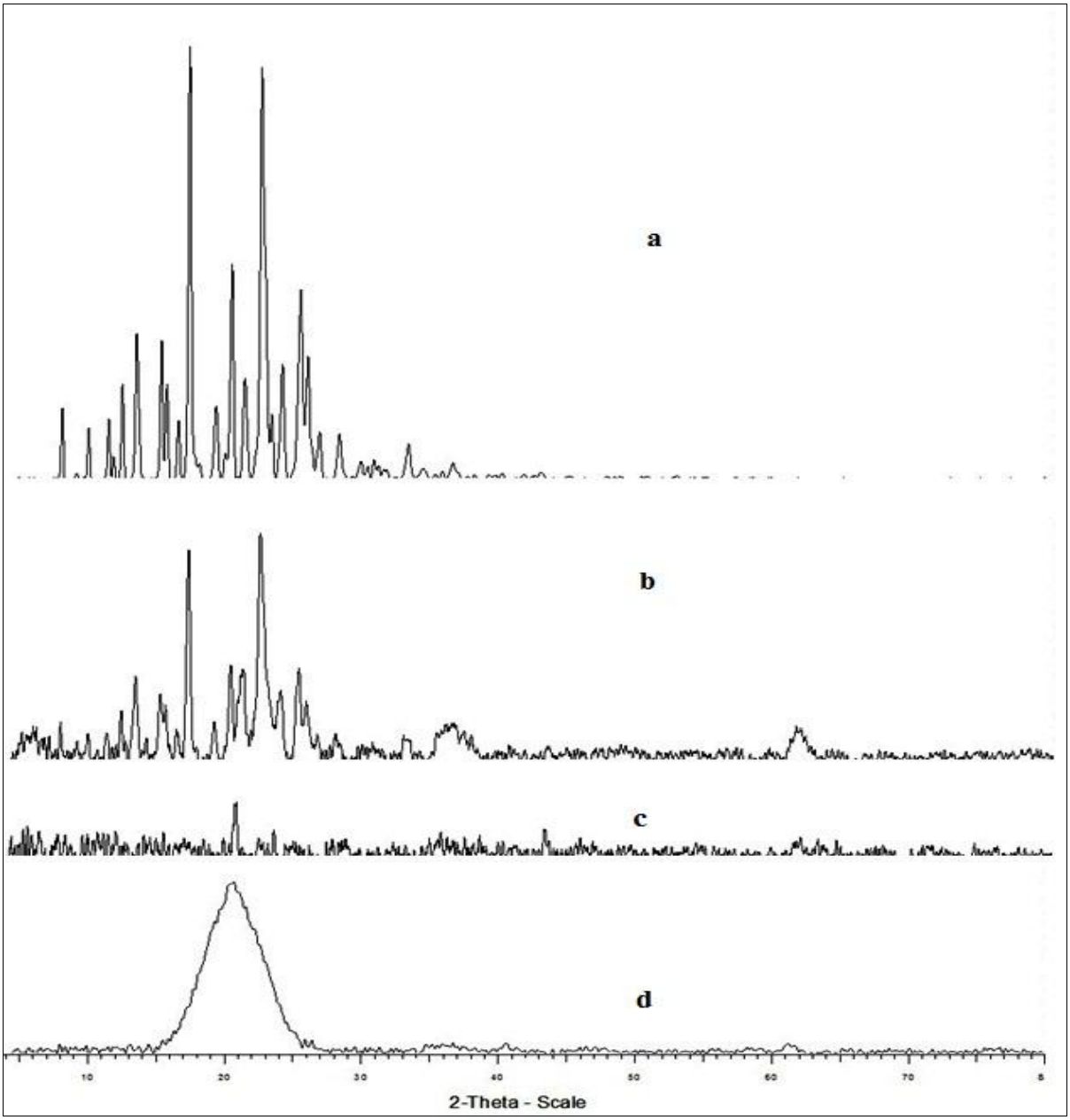

FIG.9: X-RAY POWDER DIFFRACTION SPECTRA OF (a) OLMESARTAN MEDOXOMIL (b) PHYSICAL MIXTURE OF OLM AND NEUSILIN (c) NEUSILIN AND (d) SOLID-SMEDDS

Emulsion Droplet Size

The average droplet size of the optimized liquid SEDDS, F5 as determined by photon cross correlation spectroscopy was found to be 15.92 nm at hundred times dilution. The solid self-emulsifying formulations prepared with the carriers Neusilin US2 resulted in micro emulsion with a droplet size of 26.62 nm. Thus the droplet sizes of micro emulsions formed from solid-SMEDDS were slightly higher than the liquid SMEDDS, F5. Yet there was no significant difference in the droplet sizes of micro emulsions formed by solid-SMEDDS prepared with Neusilin US2 as the carrier. Also the PDI of the two formulations were found to less than < 0.3 indicating homogenous distribution of the oil globules.

Thus Neusilin US2 served as excellent carriers with respect to retaining the droplet size of the formulation. Since droplet size plays a very crucial role in the release profile of the self- emulsifying formulations it can be concluded that the carrier Neusilin US2 will be probably able to release the drug in more or less the same manner *in-vitro* as well as *in-vivo.*

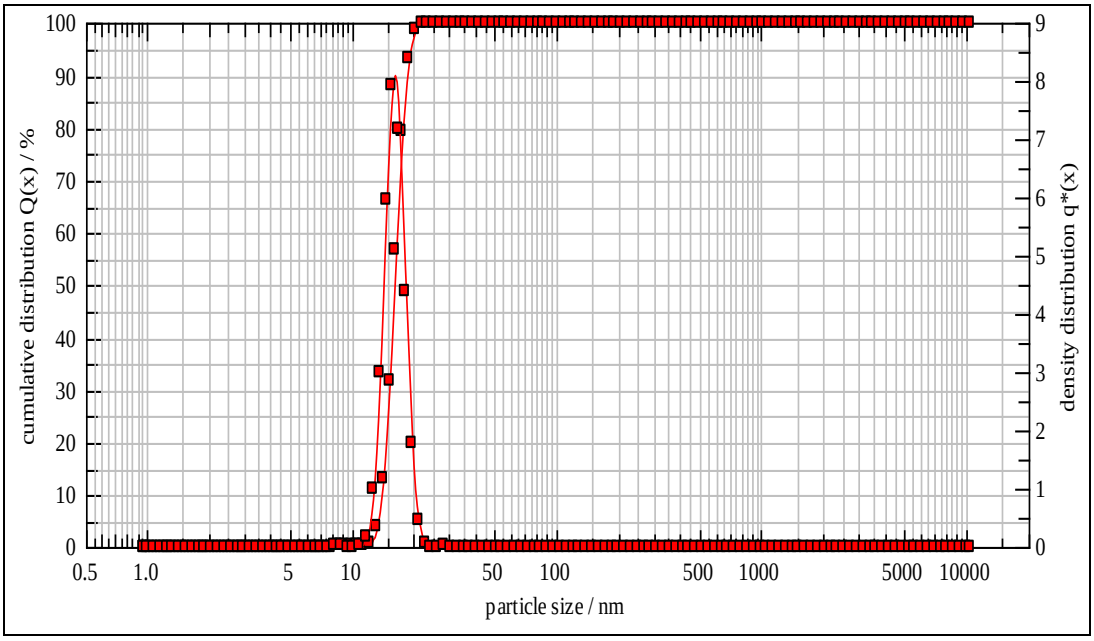

FIG.10: DROPLET SIZE DISTRIBUTION OF OPTIMIZED LIQUID SMEDDS, F5

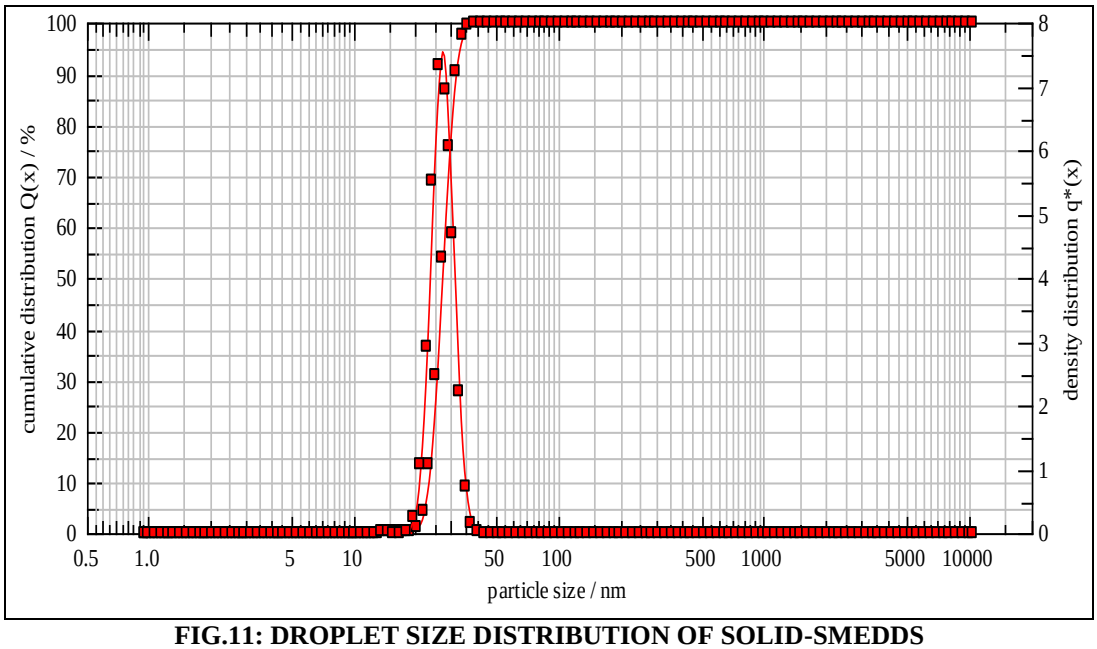

FIG.11: DROPLET SIZE DISTRIBUTION OF SOLID-SMEDDS

Drug Content Estimation:

The average drug content in the liquid SMEDDS F5 as well as solid self- micro emulsifying formulations were found to be 99.8±0.19 and 99.66±0.30 respectively. These values give indication of effective solubilization of the drug in liquid SMEDDS. Further the drug was efficiently adsorbed onto the three porous carriers which signified the excellent adsorptive ability of the carriers.

***In-Vitro* Dissolution Studies:**

Dissolution profile of pure drug and solid self micro emulsifying powder was carried out using standard conditions in pH 6.8 buffer containing 0.5 % SLS which has been shown in the **Fig.12.** As evident from the figure the solid SMEDDS showed remarkable improvement in the dissolution rate compared to pure OLM. The dissolution efficiency values (DE_{15}) and mean dissolution time (MDT) were found to 6.91±0.325 and 5.37±0.560 respectively for pure drug in comparison to 50.99 ±0.604 and 4.98±0.125 for the solid-SMEDDS. Thus the dissolution parameters were significantly higher for solid-SEDDS as compared to pure drug ($p< 0.0001$).

The faster drug release from SMEDDS is attributed due to spontaneous formation of micro emulsion due to low surface free energy at oil-water interface, which causes immediate solubilization of drug in the dissolution medium. During emulsification with water, oil, surfactant and co-surfactant effectively swells and decreases; the globule size leads to decrease in surface area and surface free energy, thus eventually increases the drug release rate.[19]

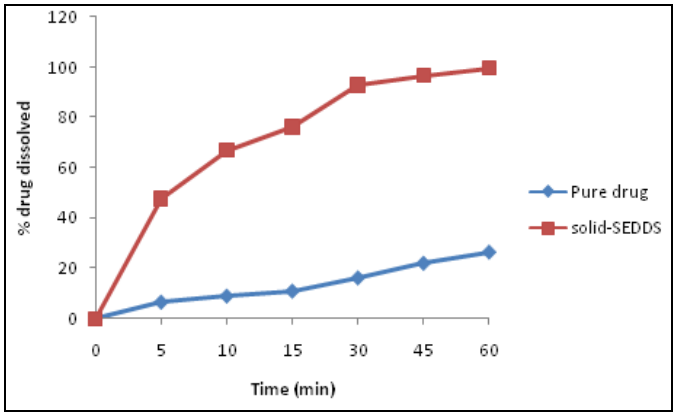

FIG.12: *IN-VITRO* DISSOLUTION PROFILES OF PURE DRUG AND SOLID-SMEDDS (Mean ± SD; n=3)

***In Vitro* Absorption Profile:**

The absorption of the drug from the everted intestinal segment of the rat is shown in the Figure 13. It was observed that the absorption of the drug was enhanced from liquid SMEDDS as 32.9± 2.5% of the drug was absorbed within 180 minutes from liquid SMEDDS in comparison to only 14.7±2.6% from that of the pure drug suspension. Solid-SMEDDS also showed improved drug absorption with comparable absorption of 29.8 ± 3.2 %within 180 minutes from self micro emulsifying powder prepared with Neusilin although the release profile was little slower as compared to the liquid SMEDDS. Thus it can be inferred that absorption of the drug from the solid-SEDDS has been enhanced and inevitably solid-SMEDDS has the potential of improved oral delivery of the drug.

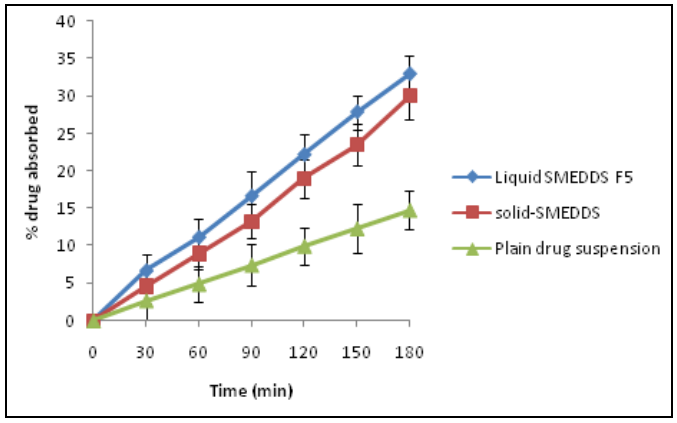

FIG.13: *IN-VITRO* ABSORPTION PROFILES OF PURE DRUG, OPTIMIZED LIQUID SMEDDS AND SOLID-SMEDDS (Mean ± SD; n=3)

CONCLUSION: In the current investigations SMEDDS of Olmesartan was prepared and evaluated for various parameters. The optimized liquid SMEDDS, F5 was successfully transformed into a free flowing powder using Neusilin US2 without affecting the self-micro emulsifying ability of the liquid SMEDDS. DSC and PXRD data of the solid self- micro emulsifying powder confirmed the solubilization of the drug in the lipid excipients and /or transformation of crystalline form of the drug to amorphous one. The enhanced in-vitro dissolution and absorption profile from the solid-SMEDDS is an indication of improvement in solubility, dissolution rate and bioavailability of the drug.

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