Formulation and Evaluation of Solid Self Micro-Emulsifying Drug Delivery System of Olmesartan medoxomil

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ABSTRACT - Olmesartan medoxomil (OLM) is a prodrug of Olmesartan, a selective AT1 subtype angiotensin-II receptor antagonist used widely for the treatment of hypertension. Although OLM has excellent performance against the treatment of hypertension, but its low bioavailability (BA), approximately 26% in humans, due to its low water solubility and efflux by drug resistance pumps in the gastrointestinal tract limits its use in pharmaceutical industry. OLM being class II drug has low solubility and thus this leads to poor absorption and low bioavailability. To increase the therapeutic efficacy of OLM, the solubility of OLM should be increased in aqueous systems. Solid Self micro-emulsifying drug delivery system (S-SMEDDS), which is easily emulsified in aqueous media under gentle agitation and digestive motility, was formulated to increase the solubility and in turn increase the oral BA of OLM. Among the surfactants, co-surfactants and oils studied, Tween 80, PEG 400 and Oleic acid were chosen for preparing SMEDDS. Liquid SMEDDS was prepared by dissolving OLM in various S_{mix} concentrations. The prepared formulations were characterized for Compatibility, Self emulsification time, Viscosity, Drug content, Dissolution studies, Droplet size, Zeta potential and Stability studies. FT-IR study revealed no interaction between drug and excipients. After evaluation, F6 formulation was found to be optimized. Thus, F6 was solidified using adsorption onto carrier technique using Aerosil 200 as adsorbent. The dissolution of the drug was enhanced significantly from the S-SMEDDS formulation as compared to pure drug. Optimized Batch SF6 showed 96.70±0.3% drug Release in 60 min while Pure Drug Showed 42.63±0.71% drug Release in 60 min. The physical state of the drug in S-SMEDDS powder was revealed by 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.

KEYWORDS – Olmesartan medoxomil, Solid self micro-emulsifying drug delivery system, Adsorption, Dissolution.

1. INTRODUCTION –

Olmesartan medoxomil (OLM), is a selective and competitive angiotensin-II receptor blocker that has been approved to treat hypertension. Chemically OLM is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-5-(2-hydroxypropan-2-yl)-2-propyl-3-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl] methyl]imidazole-4-carboxylate (figure. 1.1) [1]. It is a prodrug that is rapidly hydrolyzed to form Olmesartan by esterase's found in plasma, gastrointestinal tract, and liver during absorption. Olmesartan, the active metabolite causes dose-dependent reduction of blood pressure, vasodilation and sodium retention. However, OLM is hampered by its poor water solubility with an oral bioavailability of merely 26% in healthy humans [2]. This is due to its high lipophilicity with a Log P value of 5.55. Its poor bioavailability is also caused by the unfavourable breakage of OLM in GI fluids to Olmesartan. Olmesartan, the parent molecule, has poor permeability with a Log P of 1.2 at pH 7. Efflux pumps (P-glycoprotein) that are found in the GI tract also hamper the absorption of OLM [3].

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. [4]. Among the lipid-based system, Olmesartan medoxomil, solid self-micro emulsifying drug delivery system, is a promising technology to improve the rate and extent of **OLM** absorption of poorly water-soluble drugs.

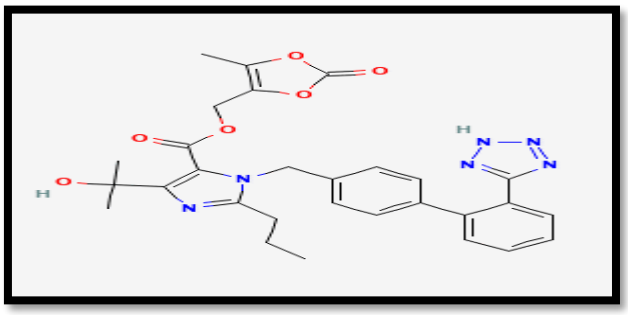


Figure 1.1 Structure of Olmesartan medoxomil

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[5]. 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 [6].

OLM being under BCS Class II, which has low solubility and high permeability require solubility enhancement as an integral part of the formulation strategies. Thus, SMEDDS are

beneficial since it is a simple process and the drugs are in a pre-dissolved state and the energy input associated with a solid–liquid phase transition is avoided, thus overcoming the slow dissolution process after oral intake[7]. Thus, OLM becomes an ideal candidate to formulate into SMEDDS to enhance the solubility and dissolution rate of the formulation, which may further increase the overall bioavailability of drug. Thus, an attempt was made to formulate a SMEDDS formulation for oral drug delivery of OLM and the liquid formulation was converted into solid for filling into capsule by adsorption onto a solid carrier technique.

2. MATERIAL AND METHOD

2.1. Material

Olmesartan medoxomil, was obtained as gift sample from CTX Life Sciences, Gujarat. Acrysol 150, & Acrysol EL-135 was Gifted sample from Corel Pharma Chem, Ahmedabad. Tween 20/60/80, Span 80, Etocas was obtained as gift sample from Croda India. PEG 400 was obtained as gift sample from BASF, India. Other excipients such as Oleic acid, Olive oil, Cottonseed oil, Sunflower oil, Soyabean oil, Arachis oil, Sweet almond oil, Coconut oil, Lemon oil, Dill oil, Coriander oil, Anise oil, Span 20, PEG 200, Propylene glycol, were purchased from Research lab, Mumbai.

2.2. Screening of Excipients

2.2.1. Solubility study [8,9,10]

The solubility of OLM in various oils, surfactants, and co-surfactants was measured, respectively. An excess amount of OLM was added into 3ml of each of the selected oils, surfactants, co-surfactants and distilled water in 5-ml stoppered vials separately, and mixed by vortexing. The mixture vials were then kept at 25 ± 1.0°C in an isothermal shaker for 72 h to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 3000 rpm for 15 min. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of OLM was determined in oils, surfactants, co-surfactants and water using UV- spectrophotometer at 256nm

2.2.2. Preliminary screening of surfactants [11]

500 µL of each surfactant was added to 500 µL of the selected oil. The mixtures were gently heated at 50 ″C for 2 min to attain homogenization. From each mixture, 100 µL were then diluted with distilled water up to 50 mL in glass stoppered flask. The stoppered flasks were inverted several times and the number of flask inversions required to form a homogenous microemulsion (with no turbidity or phase separation) was counted. Furthermore, the formed emulsions were allowed to stand for 2hr and their percentage transmittance was assessed by means of UV–Vis Spectrophotometer using distilled water as blank.

2.2.3. Preliminary screening of co-surfactants [11]

The selected oily phase and surfactant were used for further screening of the different cosurfactants (PEG 200, PEG 400) for their emulsification efficiency. Mixtures of 200 µL of cosurfactant, 400 µL of selected surfactant and 600 µL of selected oil were prepared and evaluated in the same manner as described in preliminary screening of surfactants.

2.3. Drug – Excipients Compatibility Study [12,13]

The Drug – Excipients Compatibility Studies were performed in order to confirm the drug-excipients compatibility. This study mainly include FT-IR Study. The samples of Drug and physical mixture of Olmesartan medoxomil with each excipient obtained after physical compatibility studies of one month was analysed using FTIR spectrophotometer in the range of 400–4000 cm^{-1} .The spectra so obtained were compared with spectra of pure drug for the chemical compatibility.

2.4. Construction of Pseudo-ternary phase diagram [14,15]

On the basis of the solubility studies of drug, select the oil phase, surfactants and cosurfactants. Water was used as an aqueous phase for the construction of phase diagrams. Surfactant and cosurfactant (Smix) are mixed in different weight ratios 1:1, 2:1, 3:1, 1:2. These Smix ratios were chosen in increasing concentration of surfactant with respect to cosurfactant and increasing concentration of cosurfactant with respect to surfactant for detailed study of the phase diagrams for formulation of microemulsion. For each phase diagram, oil and specific Smix ratio was mixed thoroughly in different weight ratios from 1:9 to 9:1 in different glass vials. Seventeen different combinations of oil and Smix, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 were made so as to cover possible combinations for the study to delineate the boundaries of phases precisely formed in the phase diagrams. Pseudo ternary phase diagrams were developed using aqueous titration method. Slow titration with aqueous phase was done to each weight ratio of oil and Smix and visually observed for transparent and easily flowable o/w microemulsions. The physical state of the micro- emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and cosurfactant at fixed weight ratios (Smix ratio). Based on the results, appropriate percentages of oil, surfactant and co-surfactant were selected and correlated in the phase diagram and then were used for preparation of SMEDDS. Pseudo-ternary phase diagram was constructed by using Microsoft Excel and were reported in section 3.3.

2.5. Selection of Formulation from Pseudo ternary Phase Diagram [16]

From each phase diagram constructed different formulations were selected from micro-emulsion region, so that drug could be incorporated into the oil phase on the following bases.

- The oil concentration should be such that it solubilizes the drug (single dose) completely depending on the solubility of the drug in the oil. 10 mg of OLM will dissolve easily in 1 mL of oil.
- To check if there was any effect of drug on the phase behaviour and microemulsion area of the phase diagram.
- The minimum concentration of the S_{mix} used for that amount of oil was taken.

Selected formulations were subjected to different thermodynamic stability and Dispersibility tests.

2.5.1. Thermodynamic stability studies [17,18]

1. Heating cooling cycle

Six cycles between refrigerator temperature 4^0C and 45^0C with storage at each temperature of not less than 48h was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

2. Centrifugation

Passed formulations were centrifuged at 3000 rpm for 30 min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

3. Freeze thaw cycle

Three freeze thaw cycles between -21˚C and 25 ˚C with storage at each temperature for not less than 48 h was done for the formulations.

Those formulations, which passed these thermodynamic stress tests, were further taken for the Dispersibility test for assessing the efficiency of self-emulsification.

2.5.2. Dispersibility test [19]

The efficiency of self-emulsification was assessed using a standard USP XXII dissolution apparatus 2 (Disso TDT 08L, Electrolab). One millilitre of each formulation was added to 500 mL of water at 37±0.5^{0}C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in-vitro performance of the formulations was visually assessed using the following grading system:

Grade A: Rapidly forming (within1min) Nano emulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Those formulations that passed the thermodynamic stability and also Dispersibility test in Grade A, Grade B was selected for further studies.

2.6. Preparation of Liquid SMEDDS Formulations [20]

The formulations were prepared by dissolving the formulation amount of OLM (10 mg) in the mixture of surfactant, oil and co-surfactant (Table 2.1). Oleic acid, Tween 80, Polyethylene glycol 400 (PEG 400), and OLM were accurately weighed and transferred into a borosilicate glass vial. Using magnetic stirrer, the ingredients were mixed for 10 min at 60–65^{0}C until a yellowish transparent formulation was attained. OLM SMEDDS formulations were then allowed to cool to room temperature before they were used in subsequent studies

Table 2.1- Data for Preparation of Liquid SMEDDS Formulations

Ingredients	Group I (S_{mix} 2:1)		Group II (S_{mix} 3:1)	
	F5	F6	F9	F10
OLM (mg.)	10	10	10	10
Oleic acid (% w/w)	10	20	10	20
S_{mix} (% w/w)	90	80	90	80

Where S_{mix} is Tween 80 and PEG 400

2.7 Characterization of Liquid SMEDDS

1. Appearance [17]

The prepared liquid SMEDDS were inspected visually for clarity, colour and presence of any particulate matter.

2. Determination of self-emulsification time [21]

The emulsification time of SMEDDS was determined according to United State Pharmacopeia (USP) XXIII, dissolution apparatus II. In brief, 0.5mL of each formulation was added drop wise to 500mL of purified water at 37^0C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed visually.

3. FT-IR of Liquid SMEDDS

The SMEDDS sample was analysed using FTIR spectrophotometer in the range of 400–4000 cm^{-1}. The spectra so obtained was compared with spectra of pure drug for the chemical compatibility.

4. Cloud Point [17,22]

Cloud point is the temperature above which an aqueous solution of a water-soluble surfactant becomes turbid. The Cloud point of non-ionic surfactant is the temperature at which the mixture starts to phase-separate, and two phases appear, thus becoming cloudy. Dilute the formulation 1 ml with 100 ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy or turbid. It gives the information about the stability of the microemulsion at body temperature.

5. Viscosity Determination [11]

The viscosities were measured to determine rheological properties of formulations. Brookfield viscometer with a CPE 18 spindle at 10 rpm was used to serve this purpose.

6. Robustness to dilution [23]

In order to simulate in vivo dilution behavior, effect of dilution on emulsion characteristics was studied. This test was performed by diluting 1 mL of each formula 10, 100 and 1000 times with distilled water, 0.1 N HCl and phosphate buffer pH 6.8. The diluted systems were mixed

using a magnetic stirrer at 100 rpm and 37 °C to simulate body temperature to complete homogeneity. These systems were stored at an ambient temperature for 24 h then visually observed for any signs of phase separation.

7. Determination of Refractive Index and Percent Transmittance [17,24]

The refractive index was measured using Abbes refractometer. The percent transmittance of the system is measured by diluting 1 ml of formulation with 100 fold water and % transmittance was determined using UV spectrophotometer at particular wavelength keeping distilled water as blank. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T.

8. Determination of Drug Content [14,25]

Liquid SMEDDS containing OLM, each equivalent to 10 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 to separate the undissolved excipients. The supernatant was suitably diluted and analyzed spectrophotometrically at 256 nm using UV-visible spectrophotometer.

9. Determination of Droplet size, PDI & Zeta-potential [26,27,28]

For the determination of droplet size and zeta potential the prepared formulations were suitably diluted with distilled water. To ensure complete dispersion of the formulation, the samples were inverted twice. Following complete dispersion, the mean droplet size, zeta potential (charge of surface) were directly measured using Laser Light Scattering Particle Size Analysis Technique with Zeta-Sizer. The principle involved is due to Brownian motion of droplets as a function of time which is determined due to fluctuation in light scattering, and it determined by photon correlation spectroscopy. PDI determination is done after 100 folds dilution with distilled water. The globule size distribution was expressed in terms of polydispersity index, which is a measure of the width of the globule size distribution. Zeta potential is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is negative due to presence of free fatty acids.

10. In-vitro drug release study [21]

Drug release studies from Liquid SMEDDS were performed using USP XXIII, dissolution apparatus II with 900 mL of 0.1N HCl as medium at 37 ± 0.5^0C. The speed of the paddle was adjusted to 50 rpm. Hard gelatin capsules, size 0 filled with pure drug (10 mg) and preconcentrate (equivalent to 10 mg OLM) were put into dissolution media. Samples were withdrawn at regular time intervals (5, 15, 30, 45 and 60 min) and filtered using a 0.45 μm filter. An equal volume of the dissolution medium was added to maintain the volume constant. The samples were analysed using UV spectrophotometer at 256nm.

2.8 Conversion of liquid SMEDDS into Solid SMEDDS [17]

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 Aerosil 200. Thus, the liquid SMEDDS containing OLM were adsorbed onto Aerosil 200 by mixing in a mortar and pestle till uniform distribution of blend and after sieving, it was dried and stored till evaluation tests.

2.9 Characterization of S-SMEDDS

1. Determination of micromeritic properties [17,29]

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. 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.

2. Determination of Self-emulsification time [14,17]

The emulsification time of S-SMEDDS was determined according to United State Pharmacopeia (USP) XXIII, dissolution apparatus II. In brief, S-SMEDDS formulation was added to 500mL of purified water at 37^0C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed visually

3. FT-IR of S-SMEDDS

The S-SMEDDS sample was analysed using FTIR spectrophotometer in the range of 400–4000 cm^{-1}. The spectra so obtained was compared with spectra of pure drug for the chemical compatibility.

4. Determination of Droplet size, PDI & Zeta-potential [23]

The S-SMEDDS formulations were subjected to sonication prior to globule size, zeta potential and PDI determination after 100 times dilution with distilled water. Globule size, PDI and Zeta potential was determined by photon correlation spectroscopy using Zetasizer.

5. Determination of Drug content [17]

Solid-SMEDDS containing OLM, each equivalent to 10 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 to separate the undissolved excipients. The supernatant was suitably diluted and analyzed spectrophotometrically at 256 nm.

6. In-vitro drug release study of S-SMEDDS [21]

Drug release studies from S-SMEDDS were performed using USP XXIII, dissolution apparatus II with 900 mL of 0.1N HCl as medium at 37 ± 0.5^0C. The speed of the paddle was adjusted to 50 rpm. Hard gelatin capsules, size 0 filled with S-SMEDDS (10 mg) were put into dissolution media. Samples were withdrawn at regular time intervals (5, 15, 30, 45 and 60 min)

and filtered using a 0.45 μm filter. An equal volume of the dissolution medium was added to maintain the volume constant.

7. Powder X-Ray Diffraction Study [30]

X-ray powder scattering measurements of the OLM and that of solid self- micro-emulsifying powder were carried out with X-ray diffractometer .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.

8. Scanning electron microscopy (SEM) Study [31]

Scanning electron microscopy (SEM) was used to determine the particle morphology of pure drug and optimized SMEDDS. The outer macroscopic structure of the drug and solid SMEDDS was investigated by Scanning Electron Microscope (SEM) operating at 10 kV .

2.10 Stability Study [20,32]

Stability study was conducted as per ICH guidelines for final selected solid SMEDDS formulation. Hard Gelatin Capsule filled with final selected solid SMEDDS of Olmesartan medoxomil were stored in air-tight screw capped containers protected from light and maintained under real time (25 ± 2 ºC / 60± 5% RH) for 3 months. Samples were taken on 30th day, 60th day , 90 th day and evaluated for appearance, self-emulsifying properties and drug content. The results are reported in section 10.11.

3. RESULT AND DISCUSSIONS

3.1. Screening of Excipients

3.1.1. Solubility study

The self-emulsifying formulations consisted of oil, surfactants, co-surfactants and drug should be clear and monophasic liquids at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution. Solubility studies were aimed at identifying suitable oily phase and surfactant/s for the development of OLM SMEDDS. Identifying the suitable oil, surfactant/cosurfactant having maximal solubilizing potential for drug under investigation is very important to achieve optimum drug loading . The solubility of OLM in various oily phases, surfactants and cosurfactant is reported in Table 3.1, 3.2, 3.2 respectively and it is represented graphically in Figure 3.1

The Solubility study demonstrated that solubility of the lipophilic drug-Olmesartan medoxomil was found to be highest in Oleic Acid followed by Anise oil. All the surfactants showed good solubility of the drug. Among the surfactants tested in this study, Tween 80, with HLB 15 was selected as appropriate surfactant because non-ionic surfactants are less toxic than ionic surfactants, has good biological acceptance, is powerful permeation enhancer, is less affected by pH and ionic strength, and highest solubility was also obtained. Furthermore,

Polyethylene glycol 400 (PEG 400) was selected as a co-surfactant because of their potential to solubilize the drug.

Table 3.1 - Data for Solubility study of OLM in Various Oils

Sr No	Oil	Solubility of OLM (mg/ml)
1	Olive oil	4.07
2	Cottonseed oil	4.41
3	Sunflower oil	3.23
4	Oleic acid	11.70
5	Arachis oil	5.68
6	Sweet almond oil	4.36
7	Coconut oil	2.92
8	Lemon oil	6.69
9	Dill oil	10.08
10	Coriander oil	9.82
11	Anise oil	10.35
12	Soyabean oil	3.20

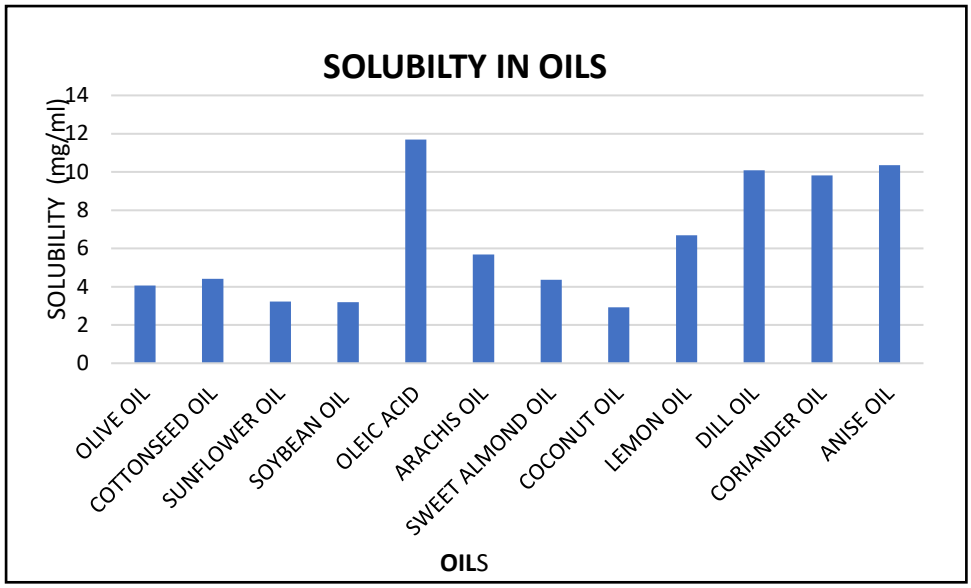
Table 3.2 - Data for Solubility study of OLM in Various Surfactants

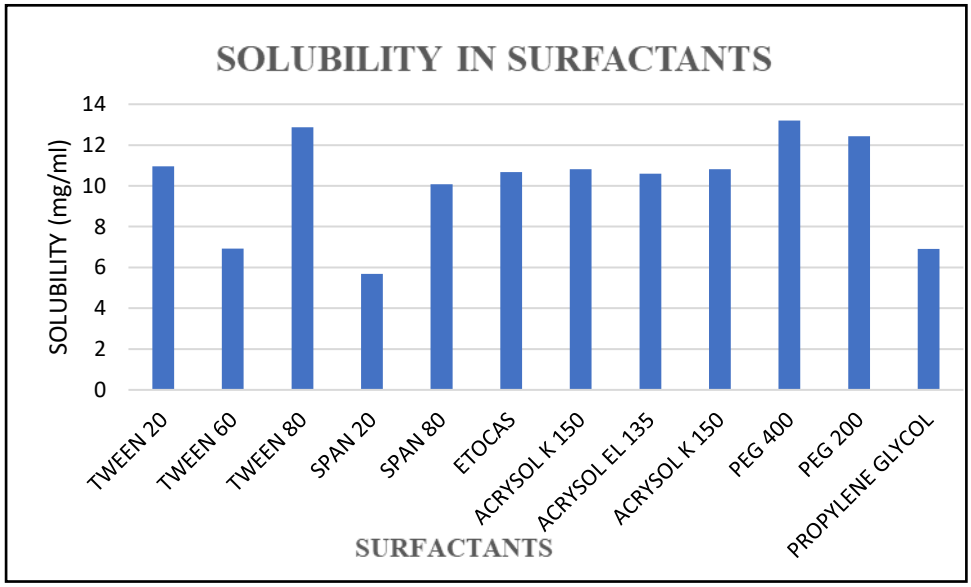
Sr No	Surfactant	Solubility of OLM (mg/ml)
1	Tween 20	10.95
2	Tween 60	6.92
3	Tween 80	12.87
4	Span 20	5.68
5	Span 80	10.08
6	Etocas 35	10.68
7	Acrysol EL 135	10.59
8	Acrysol K 150	10.82

Table 3.3 - Data for Solubility study of OLM in Various Co-Surfactants

Sr No	Co-Surfactant	Solubility of OLM (mg/ml)

1	PEG 200	12.44
2	PEG 400	13.20
3	Propylene Glycol	6.91





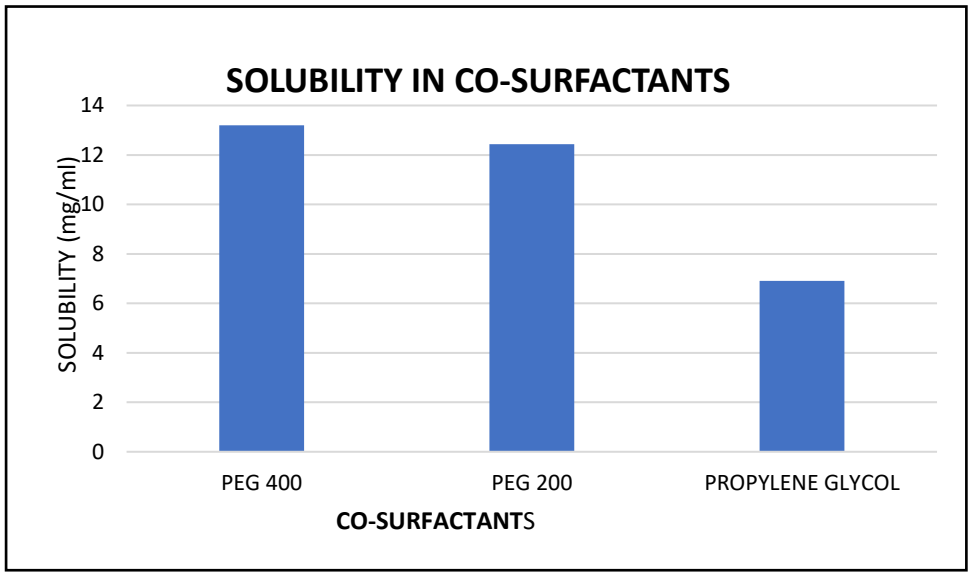


Figure 3.1 – Solubility of OLM in various Oils, Surfactants and Co-surfactants

3.1.2. Preliminary screening of surfactants

Non-ionic surfactants are generally considered less toxic than ionic surfactants. They are usually accepted for oral ingestion. The surfactants were compared for their emulsification efficiencies using oily phase. It has been reported that well formulated SMEDDS is dispersed within seconds under gentle stirring. Transmittance values of different mixtures are demonstrated in Table 3.4. From results it was inferred that the oily phase Oleic acid exhibited the highest emulsification efficiency with Tween 80, requiring only 5 flask inversions for homogenous emulsion formation. Therefore, mentioned results suggested the use of Oleic acid as an oily phase with Tween 80 as a surfactant for further study.

Table 3.4 - Data for Emulsification efficiency of surfactant

Sr. No.	Oils	% Transmittance
		Oleic acid
1.	Tween 80	96.52±0.27
2.	Tween 20	90.15±0.33

3.1.3. Preliminary screening of co-surfactants

Addition of a co-surfactant to the surfactant-containing formulation was reported to improve dispersibility and drug absorption from the formulation. In view of current investigation, two co-surfactants, Polyethylene Glycol 400, Polyethylene Glycol 200 were compared for ease of emulsification. As reported in Table 3.5, Oleic acid exhibited good emulsification with both co-surfactants, with PEG 400 showing maximum transmittance followed by PEG 200.

Table 3.5 - Data for Emulsification efficiency of Co-surfactant

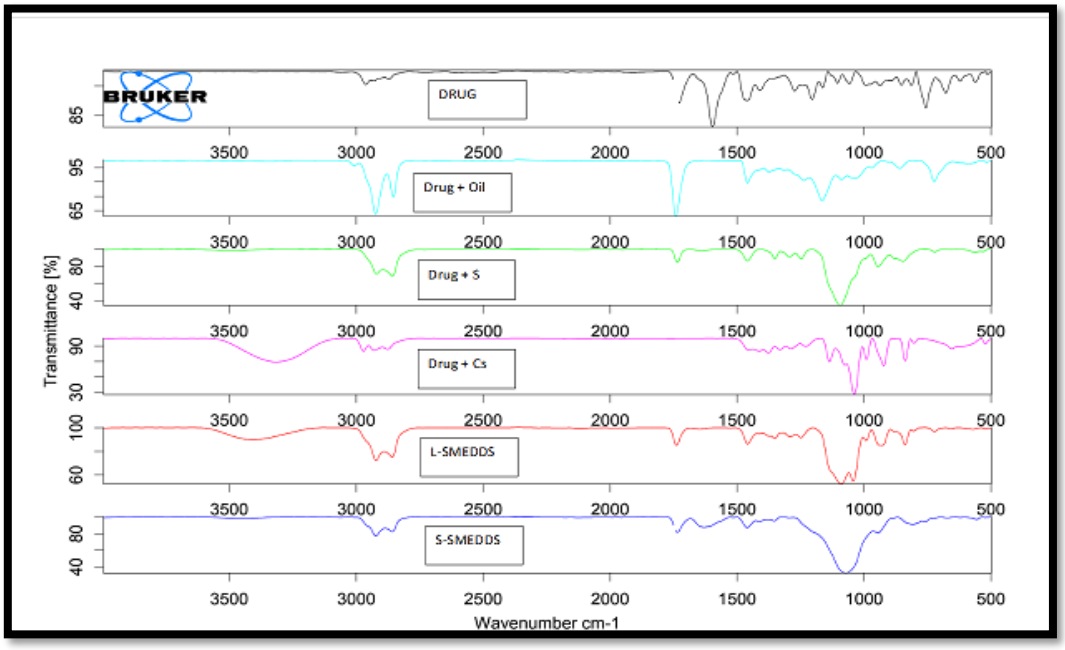
Sr. No.	Co-surfactants	% Transmittance
		Oleic Acid + Tween 80
1.	PEG 400	97.79±0.28
2.	PEG 200	93.32±0.17

Based on the results of preliminary screening, one distinct system was selected which was: **Oleic acid** as oily phase, **Tween 80** as surfactant, **Polyethylene Glycol 400** as co-surfactant.

3.2. Drug – Excipients Compatibility Study

Compatibility of drug and excipients was determined by FT-IR Spectroscopical analysis and drug and excipients were found to be compatible and is shown in figure 3.2

Figure 3.2 – FT-IR Spectra of OLM and Excipients and SMEDDS



3.3. Construction of Pseudo ternary phase diagram

The consideration for screening formulation of SMEDDS usually involves: the formulation composition should be simple, safe, and compatible; it should possess good solubility; a large efficient self-emulsification region which should be found in the pseudo-ternary phase diagram, and have efficient droplet size after forming microemulsion. Thus, pseudo-ternary phase diagrams were constructed to identify the Self-micro-emulsifying regions with maximum drug loading and to optimize the concentration of oil, surfactant and co-surfactant in the SMEDDS formulations and to obtain transparent and stable O/W micro-emulsions.

The shaded areas in the pseudo-ternary phase-diagrams shown in below figures represented the existence field of stable, clear and transparent O/W micro-emulsions containing Oleic acid as oil and with the Tween 80: PEG 400 fixed mixing ratio, respectively. For any selected composition of surfactant and co-surfactant ratio from self micro-emulsifying region of ternary phase diagram (shaded) the addition of great volumes of continuous phase allowed the clear system.

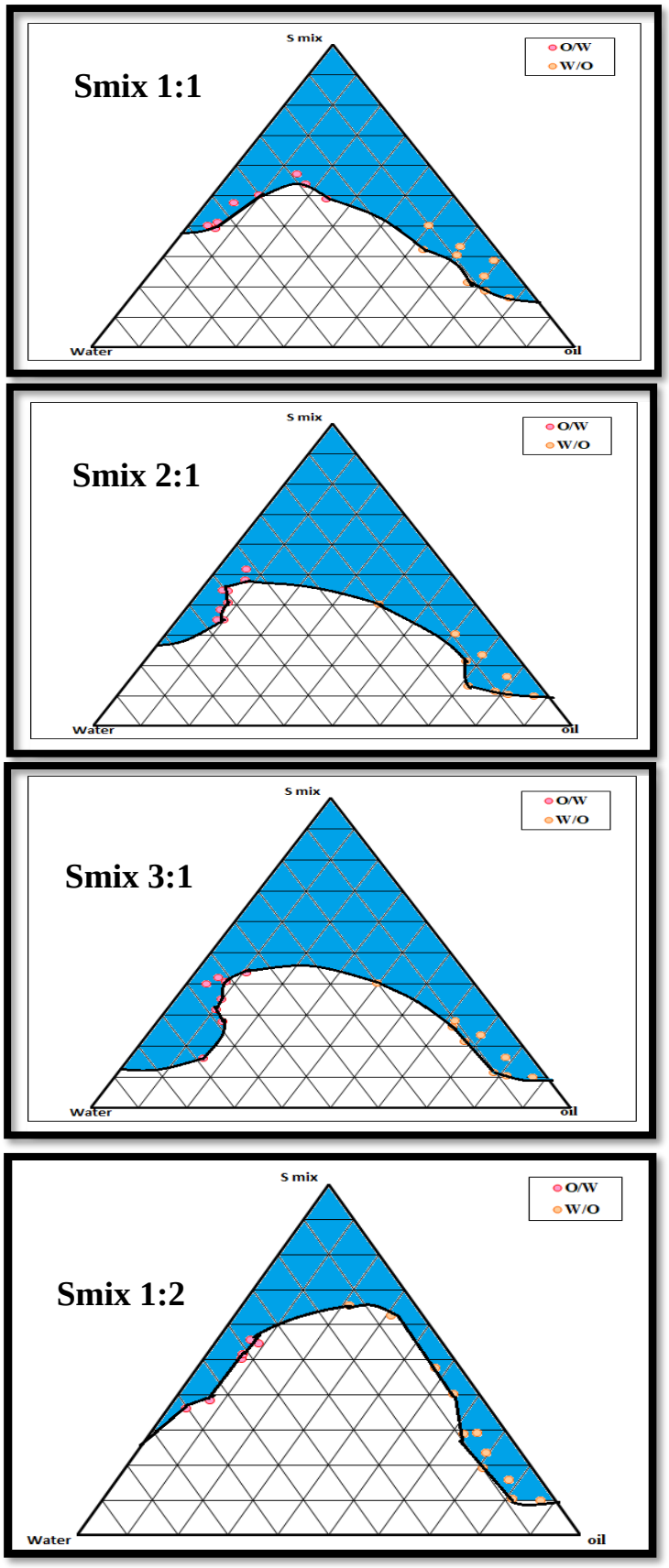


Figure 3.3 -Pseudo ternary Phase diagram of Oleic acid(oil)-S_{mix} (Tween 80 and Polyethylene glycol 400) and water system having different S_{mix} ratio.

It can be seen that these phase diagrams contained different areas of clear and isotropic microemulsion region. It can be also seen that microemulsion region exists at S_{mix} ratio 1:1. Increasing the concentration of surfactant (2:1) resulted in even larger area of microemulsion region. Further increasing surfactant concentration from 2:1 to 3:1 resulted in slight influence on microemulsion region . The influence of concentration of co-surfactant on the microemulsion region was also seen by constructing the phase diagram in ratio of 1:2. It was seen that the region of microemulsion was decreased with increase in concentration of co-surfactant.

The existence of large or small microemulsion region depends on the capability of a particular surfactant or surfactant mixture to solubilize the oil phase. The extent of solubilization resulted in a greater area with clearer and homogenous solution. It was seen that when the surfactant (Tween 80) was used alone, the oil phase was solubilized to a lesser extent at higher concentration of surfactant implying that surfactant alone was not able to reduce the interfacial tension of oil droplet to a sufficiently low level and thus was not able to reduce the free energy of the system to an ultra-low level desired to produce microemulsions. When a co-surfactant was added, the interfacial tension was reduced to a very low level and very small free energy was achieved which helps in larger microemulsion region. With further increase in surfactant from 1:1 to 2:1 and 3:1 further drop in interfacial tension and free energy was achieved resulting in maximum region of microemulsion formation. Thus, pseudo-ternary phase diagram for **S_{mix} 1:1, 2:1 and 3:1** were selected for the formation of drug loaded self micro-emulsifying drug delivery system.

3.4. Selection of Formulation from Pseudo ternary Phase Diagram

It is well known that large amounts of surfactants cause GI irritation; therefore, it is important to determine the surfactant concentration properly and use minimum concentration in the formulation. S. Shafiq et al. reported the basis of selecting different microemulsion formulations from the phase diagram, as hundreds of formulations can be prepared from microemulsion region of the diagram. From the data shown in different pseudo-ternary phase diagrams ,it was understood that oil could be solubilized up to the extent of 50% w/w. Therefore, from phase diagram with different concentrations of oil, which formed microemulsions, were selected at a difference of 10% (10, 20, 30, 40%) so that maximum formulations could be prepared covering the microemulsion/ self emulsification area of the phase diagram. For each percentage of oil selected, only those formulations were taken from the phase diagram, which needed minimum concentration of S_{mix}. There was no sign of change in the phase behaviour and microemulsion area of phase diagrams when Olmesartan medoxomil was incorporated in the formulations, which indicated the formation and stability of microemulsions consisting of non-ionic components is not affected by the pH and or ionic strength.

3.4.1. Thermodynamic stability studies

Microemulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. It is the thermostability which differentiates nano- or microemulsion from emulsions that have kinetic stability and will eventually phase separate. Thus, the selected formulations were subjected to different thermodynamic stability testing by using heating cooling cycle,

centrifugation and freeze thaw cycle stress tests. Those formulations, which passed thermodynamic stability tests, were taken for dispersibility test. Thus, it was concluded that the efficiency of surfactant and co-surfactant mixture was unaffected after exposing to extreme conditions.

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3.4.2. Dispersibility test

When infinite dilution is done to micro-emulsion formulation, there is every possibility of phase separation, leading to precipitation of a poorly soluble drug as micro-emulsions are formed at a particular concentration of oil, surfactant and water. For oral micro-emulsions the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC.

In the present study, we used distilled water as a dispersion medium because it is well reported that there is no significant difference in the micro-emulsion prepared using non-ionic surfactants, dispersed in either water or simulated gastric or intestinal fluid Formulations in **Group I** ,**Group II**, **Group III** that passed dispersibility test in Grade A, B and C were taken for further study, as Grade A and B formulations will remain as nano emulsions when dispersed in GIT. Formulation falling in Grade C could be recommended for self-emulsifying drug delivery formulation.

So, from the study, total 4 formulations were selected for further study 2 each from **Group II**, **Group III.**

Table 3.6: Data for Thermodynamic stability test and Dispersibility of different formulations from Group 1

Group I S_{mix} ratio 1:1	**Percentage w/w of different components in formulation**		**Observations based on the preparation, thermodynamic stability studies and dispersibility tests**				**Inference**
Formulations	**Oil**	**S_{mix}**	**H/C**	**Cent.**	**Freez. Tha.**	**Dispers e.**	
F1	20	80	√	√	X	Grade B	Rejected
F2	25	75	√	X	X	Grade C	Rejected
F3	30	70	√	X	X	Grade C	Rejected
F4	35	65	X	X	X	Grade D	Rejected

Table 3.7: Data for Thermodynamic stability test and Dispersibility of different formulations from Group 2

Group I S_{mix} ratio 2:1	**Percentage w/w of different components in formulation**		**Observations based on the preparation, thermodynamic stability studies and dispersibility tests**				**Inference**
Formulations	**Oil**	**S_{mix}**	**H/C**	**Cent.**	**Freez. Tha.**	**Dispers e.**	
F5	20	80	√	√	√	Grade A	Selected
F6	25	75	√	√	√	Grade A	Selected
F7	30	70	√	X	X	Grade C	Rejected
F8	35	65	X	X	X	Grade C	Rejected

Table 3.8: Data for Thermodynamic stability test and Dispersibility of different formulations from Group 3

Group I S_{mix} ratio 3:1	**Percentage w/w of different components in formulation**		**Observations based on the preparation, thermodynamic stability studies and dispersibility tests**				**Inference**
Formulations	**Oil**	**S_{mix}**	**H/C**	**Cent.**	**Freez. Tha.**	**Disper se.**	
F9	20	80	√	√	√	Grade A	Selected
F10	25	75	√	√	√	Grade B	Selected
F11	30	70	√	X	X	Grade C	Rejected
F12	35	65	X	X	X	Grade C	Rejected

Where, Heating cooling cycle (H/C).

Freeze-thaw cycle (Freez. Tha.).

Centrifugation (Cent.).

Dispersibility test (Disperse.)

3.5. Preparation of Liquid SMEDDS Formulations

Formulations selected in section 2.6 were prepared as per the composition reported in Table 2.1 and found to be thermodynamically stable even after addition of a drug.

3.6. Evaluation of Liquid SMEDDS Formulations

1. Appearance

The prepared SMEDDS were inspected visually and found to be clear without presence of any particulate matter.

2. Determination of Self emulsification time

The rate of emulsification is an important index for the assessment of the efficiency of emulsification that is the SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The emulsification time of liquid SMEDDS are presented in Table 3.9. Emulsification time study showed that all the formulations emulsified within 30 s. Among the tested formulations, F6 and F9 showed shortest emulsification time than others.

3. FT-IR of liquid SMEDDS

FT-IR spectrum is reported in Fig 3.2. The scanning range was 400 to 4000 cm-1 and resolution was 1cm-1 . So, from the spectra of pure drug OLM and the Liquid SMEDDS it can be concluded that all the characteristic peaks of OLM were present in the Liquid SMEDDS spectrum.

4. Determination of Cloud point

Cloud points of all formulation are given in Table 3.9 Knowing the cloud point is important for:

- Determining storage stability, storing formulations at temperatures significantly higher than the cloud point may result in phase separation and instability.
- Generally, non-ionic surfactants show optimal effectiveness when used near or below their cloud point.
- Wetting, cleaning and foaming characteristics can be different above and below the cloud point.
- Its gives information about stability of microemulsion at body temperature.

5. Determination of Viscosity

The rheological properties of the SMEDDS are evaluated by Brookfield viscometer. These viscosities determination confirm whether the system is w/o or o/w. If system has low viscosity, then it is o/w type of the system and if high viscosities then it are w/o type of the system. The F6 formulation shows the lowest viscosity. The results of all formulation are given in table 3.9.

6. Robustness to Dilution

In order to simulate in vivo dilution behavior, effect of dilution on emulsion characteristics was studied. 1 mL of each formulation was diluted with 10, 100 and 1000 times with distilled water, 0.1 N HCl and phosphate buffer pH 6.8. These systems were stored at an ambient temperature for 24 h then visually observed for any signs of phase separation. The results of all formulation are given in table 3.10.

Table 3.9 - Data for Evaluation of Liquid SMEDDS formulations

Evaluation Parameters	Group 2 (S_{mix} 2:1)		Group 3 (S_{mix} 3:1)	
	F5	F6	F9	F10
Self-Emulsification time[a] (sec)	18.66±1.24	13.66±1.24	15.33±1.24	16.66±1.24
Cloud point (^{0} c)	79	87	85	82
Viscosity (cps)[a]	53.39±0.54	46.23±0.77	49.06±0.62	53.76±0.61

[a]Mean ± SD, n = 3

Table 3.10. Data for Robustness to dilution of liquid SMEDDS

Sr No	Groups	Formulations	Distill water			0.1 N HCl			6.8 pH Buffer		
			10	100	1000	10	100	1000	10	100	1000
1	Group 2 Smix (2:1)	F5	√	√	√	√	√	√	√	√	√
2		F6	√	√	√	√	√	√	√	√	√

3	**Group 3 Smix (3:1)**	**F9**	√	√	√	√	√	√	√	√	√
4		**F10**	√	√	√	√	√	√	√	√	√

7. Determination of Refractive Index and Percent Transmittance

The refractive index measured using Abbes refractometer. Refractive indexes and % transmission of all formulations are shown in following table 3.11.

8. Determination of Drug Content

The drug content of all formulations ranged between 98.61±0.12 to 96.57±0.27 % and passed uniformity of content. The drugs content of F6 formulation was found to be 98.61% while other formulation drug content found less than 98% so it was concluded that F6 formulation have more drug content as compare to others. The results are reported in table 3.11.

Table 3.11 - Data for Evaluation of Liquid SMEDDS formulations

Evaluation Parameters	**Group 2 (S_{mix} 2:1)**		**Group 3 (S_{mix} 3:1)**	
	F5	**F6**	**F9**	**F10**
Refractive Index [a]	1.43±0.01	1.46±0.02	1.44±0.01	1.46±0.007
% Transmittance [a]	93.32±0.17	98.39±0.18	97.56±0.27	95.34±0.27
Drug Content [a] %	96.57±0.27	98.61±0.12	97.90±0.13	97.81±0.13

[a]Mean ± SD, n = 3

9. Determination of Droplet size, PDI & Zeta-potential

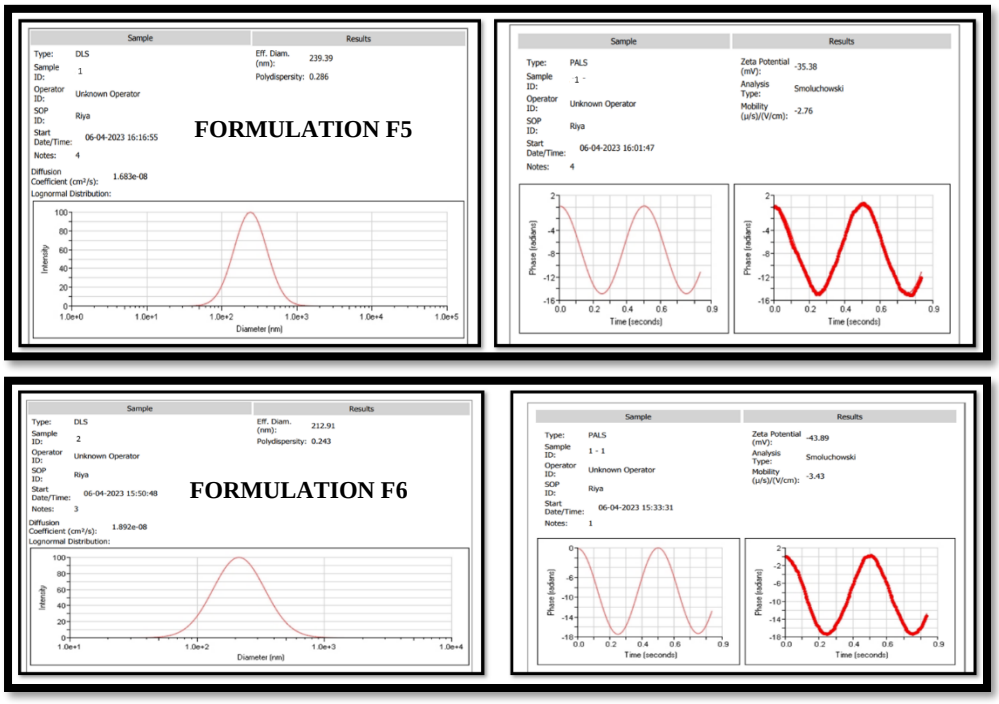
The droplet size of the emulsion is a crucial factor in self-emulsification process because it determines the rate and extent of drug release as well as drug absorption. Also, it has been reported that the smaller particle size of the emulsion dro1plets may lead to more rapid absorption as well as enhance the bioavailability of the formulation. The batch F6 was with mean particle size 212.91 nm in water. The resulting microemulsion produced was with a small mean size and a narrow particle size distribution regardless of the dispersion medium. The charge of SMEDDS is another important property that should be assessed. All formulations were diluted with purified water to avoid error caused by the dispersion medium and the zeta-

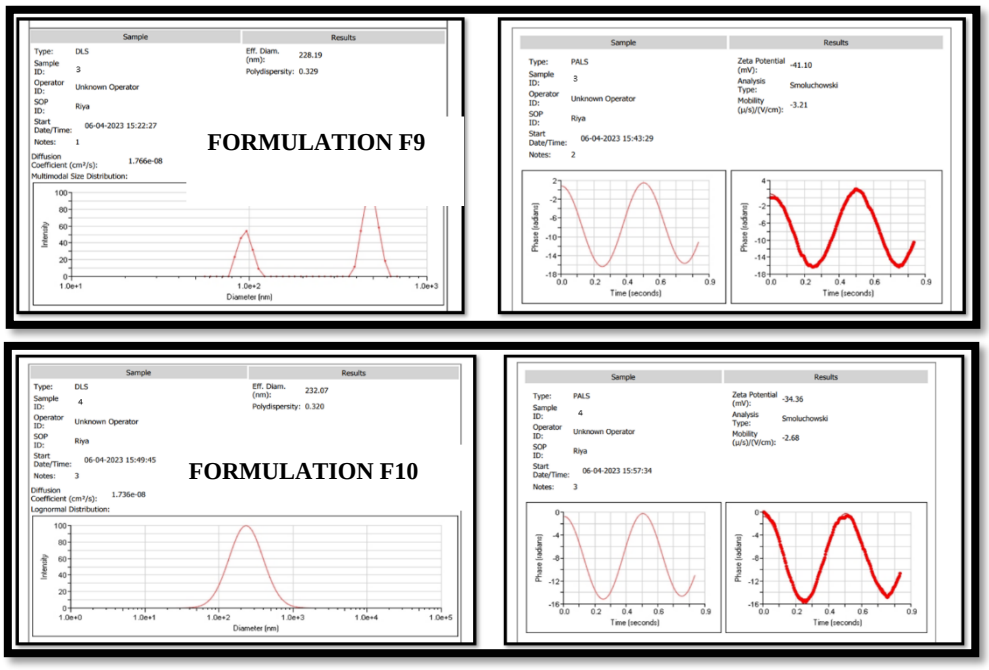
potential of the resulting emulsions was measured. The blank SMEDDS formulation exhibited almost no charged emulsion whereas a negatively charged emulsion was obtained with drug-loaded SMEDDS. This may be because the emulsifier used in the formulation was a non-ionic-surfactant. The batch F6 had the zeta potential i.e. -43.89 mV with highest zeta potential towards negative side. The zeta potential governs the stability of microemulsion, it is important to measure its value for stability samples. The high value of zeta potential indicates electrostatic repulsion between two droplets. DLVO theory states that electric double layer repulsion will stabilize microemulsion where electrolyte concentration in the continuous phase is less than a certain value.

Table 3.12. Data for Droplet size, PDI & Zeta-potential of liquid SMEDDS

Evaluation Parameters	Group 2 (S_{mix} 2:1)		Group 3 (S_{mix} 3:1)	
	F5	F6	F9	F10
Droplet size (nm)	239.39 nm	212.91 nm	228.19 nm	232.07 nm
PDI	0.286	0.243	0.329	0.320
Zeta-potential (mV)	-35.38 mV	-43.89 mV	-41.10 mV	-34.36 mV

Figure 3.4 - Results of Droplet size distributions and zeta potential of Liquid SMEDDS





10. In-vitro Drug Release Study

The *in- vitro* drug release study of liquid SMEDDS were performed in 0.1N HCl. The percent drug release for different formulations is shown in **Table 3.13**. In the self-micro emulsifying systems, the free energy required to form an emulsion was very low, thereby allowing spontaneous formation of an interface between the oil droplets and water. It is suggested that the oil/surfactant/co-surfactant and water phases effectively swell and eventually there was increase in the release rate. The in-vitro release was examined for optimized formulation F6 and F9 was performed. It was clear from the **Figure 3.5** that the maximum percentage of the drug released within 15min because of fast emulsification.

The SMEDDS represented in solubilized form in gastric fluids after ingestion and hence provided large interfacial area for Olmesartan medoxomil. Therefore, the optimized formulations (F6 and F9), had higher drug release than Plain drug OLM. **Among F6 and F9, the F6 formulation showed highest drug release with least particle size, so F6 is considered to be the best formulation and thus will be converted into solid SMEDDS.**

Table 3.13 Dissolution data for Drug and Liquid SMEDDS formulations in 0.1N HCl

Time (min)	Percent drug released [a]		
	Pure Drug	F6	F9
00	00	00	00

05	6.27±0.31	82.31±0.61	81.64±0.31
15	17.89±0.82	87.40±0.40	84.91±0.20
30	30.11±0.51	92.61±0.51	90.77±0.40
45	37±0.40	97.40±0.20	92.20±0.31
60	42.63±0.71	98.60±0.31	95.36±0.35

[a] Represents mean ± S.D. (n = 3)

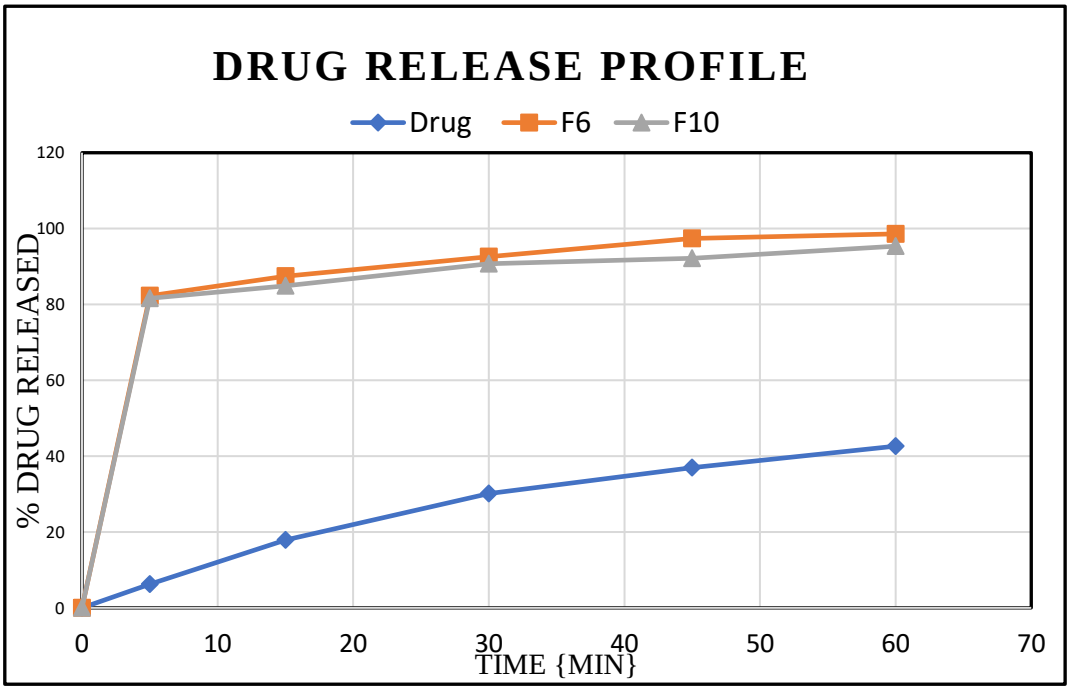


Figure 3.5. In- vitro drug release profile of Pure drug [OLM] and Liquid SMEDDS Formulations in 0.1N HCl

3.7. Conversion of liquid SMEDDS into Solid SMEDDS

Solid SMEDDS were prepared as per the composition reported in **Table 3.14.** Formulation 6 was selected for converting into S-SMEDDS**.**

Table 3.14: Data for Preparation of Solid SMEDDS Formulation

Adsorbent	Amount of Liquid SMEDDS (ml)	Amount of adsorbent required to get free flow powder (g)
Aerosil 200	10 ml	2.5 g

3.8 Characterization of S-SMEDDS

1. Determination of Micromeritic properties

Results of powder characteristics are given below, in **Table 3.15**

Table 3.15. Data for micromeritic properties of S-SMEDDS

Formulation Code	Angle of Repose (degree)	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
SF6	27.9 degree	0.5 g/ml	0.55g/ml	9.09	1.111

2. Determination of Emulsification time

S-SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The emulsification time of S-SMEDDS are presented in **Table 3.16**

Table 3.16. Data for Emulsification time of S-SMEDDS

Evaluation Parameters	SF6
Self Emulsification Time (sec) [a]	19±0.8

[a] Represents mean ± S.D. (n = 3)

3. FT-IR of Solid SMEDDS

FT-IR spectrum is reported in Fig 3.2. The scanning range was 400 to 4000 cm-1 and resolution was 1cm-1 . So, from the spectra of pure drug OLM and the Solid SMEDDS it can be concluded that all the characteristic peaks of OLM were present in the Solid SMEDDS spectrum.

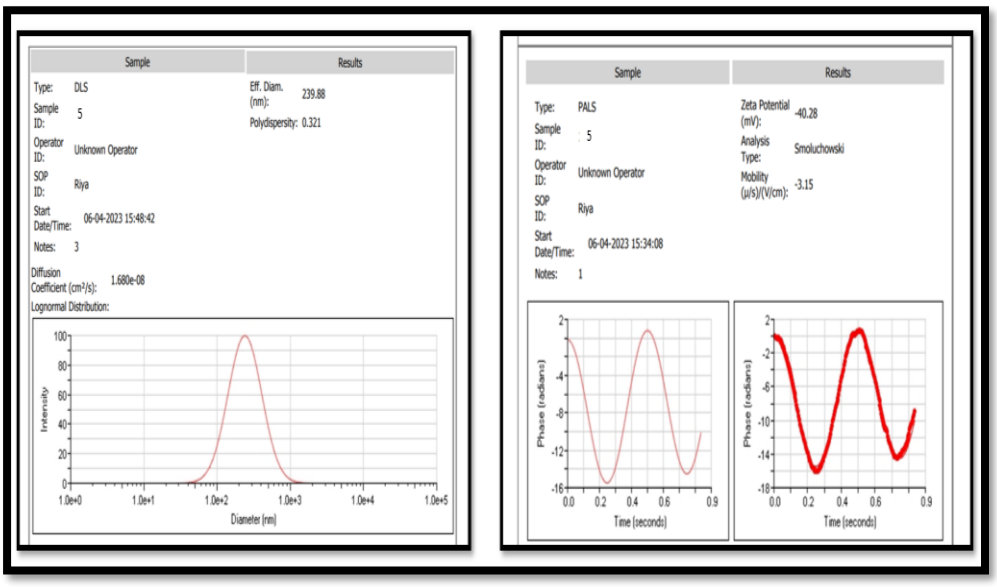
4. Determination of Droplet size, PDI & Zeta-potential

Globule size, PDI and Zeta potential was determined by photon correlation spectroscopy using Zetasizer. The results are reported below

Table 3.17. Data for Droplet size, PDI & Zeta-potential of liquid SMEDDS

Evaluation Parameters	SF6
Droplet size (nm)	239.88 nm
PDI	0.321
Zeta-potential (mV)	-40.28 mV

Figure 3.6 - Results of Droplet size distributions and zeta potential of S-SMEDDS



5. Determination of Drug Content

The drug content of SF6 formulation is given below,

Table 3.18. Data for Drug Content of S-SMEDDS

Evaluation Parameters	SF6
Drug Content %	98.23±0.11

[a]Represents mean ± S.D. (n = 3)

6. In-vitro drug release study of S-SMEDDS

The *in-vitro* drug release studies were performed in order to ensure the quick release of the drug in the dissolution medium. *In-vitro* dissolution studies also give an idea about the self-emulsification efficiency of the developed system. The *in-vitro* drug release profile of was evaluated in 0.1N HCl (n = 3). It was observed that both the solid SMEDDS formulations SF6 released more than 90% of Olmesartan medoxomil within 60 min. The formulation dispersed almost instantaneously indicating the high self-emulsion efficiency of the developed formulations.

The graph of the drug release profile is shown in **Figure 3.6**. OLM from the solid SMEDDS was completely and rapidly dissolved in medium without affecting the dissolution pattern also.

Table 3.19: Dissolution data for S-SMEDDS in 0.1N HCl

Time (Minute)	Percent drug dissolved [a]	
	Pure Drug	**SF6**
00	00	00
05	6.27±0.31	75.29±0.4
15	17.89±0.82	78.54±0.5
30	30.11±0.51	82.89±0.3
45	37±0.40	86.99±0.3
60	42.63±0.71	96.70±0.3

[a] Represents mean ± S.D. (n = 3)

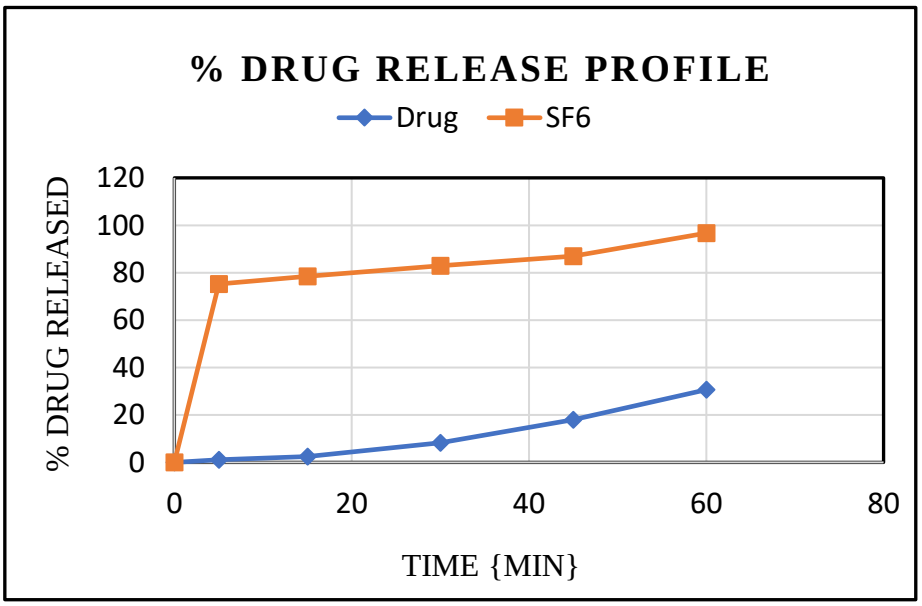


Figure 3.6:- *In- vitro* drug release profile of Solid SMEDDS

10.10.6 X-ray Powder Diffraction (XRPD) Study

The PXRD patterns of pure drug (OLM) and S-SMEDDS (SF6) were presented in **Figure 10.31 and 10.32**. The XRPD patterns of pure drug OLM showed numerous sharp peaks which are the characteristic of a crystalline compound. And these peaks are absent in the PXRD pattern of S-SMEDDS indicating the transformation crystalline nature to Amorphous nature.

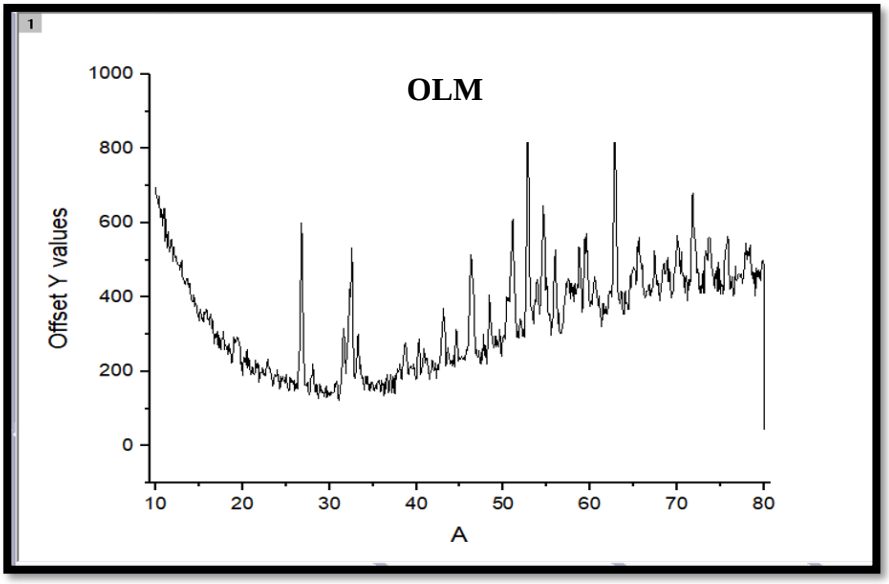


Figure 3.7 XRPD of Olmesartan medoxomil

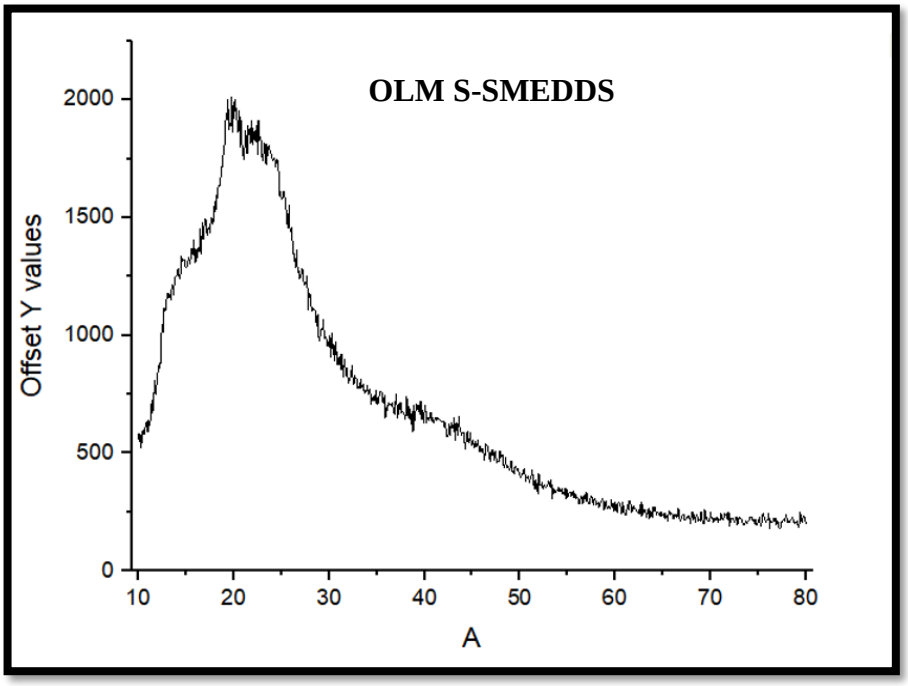


Figure 3.8 XRPD of S-SMEDDS (SF6)

10.10.7 Morphological analysis {Scanning Electron Microscopy}

The surface morphology of the pure drug and solid SMEDDS were examined by the SEM and the images are represented in **figure 10.33 and 10.34.** SEM revealed OLM as crystalline powder with irregular shaped crystals. The typical crystalline structure of Olmesartan medoxomil was absent in S-SMEDDS of OLM, which indicates the transformation of the drug from crystalline state to amorphous state i.e. the drug is completely solubilised in oil phase of L-SMEDDS. The S-SMEDDS appeared as smooth 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 Aerosil 200. The figure clearly illustrates that there are no signs of coalescence, indicating thereby the enhanced physical stability of the formulation.

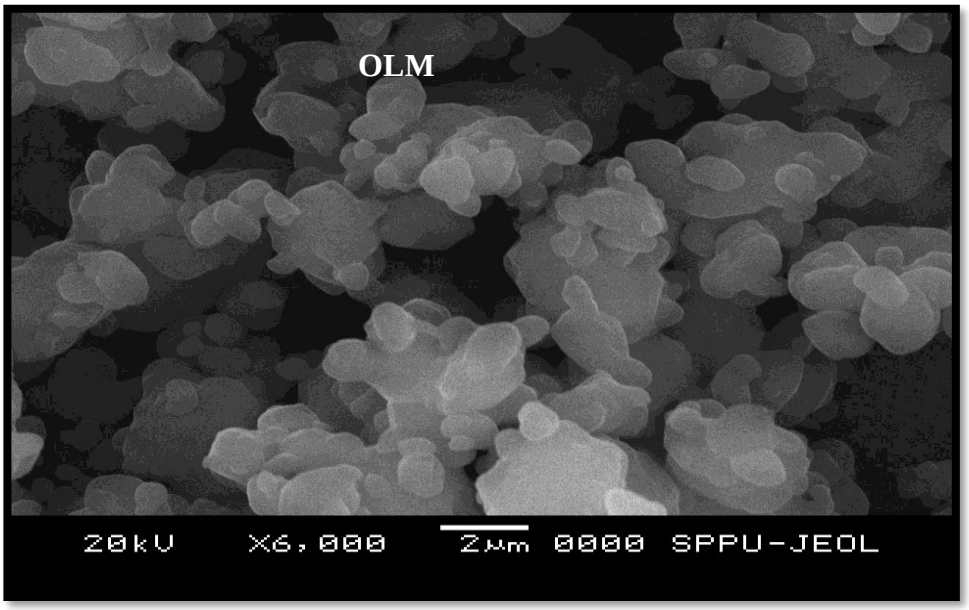


Figure 3.9 SEM of Olmesartan medoxomil

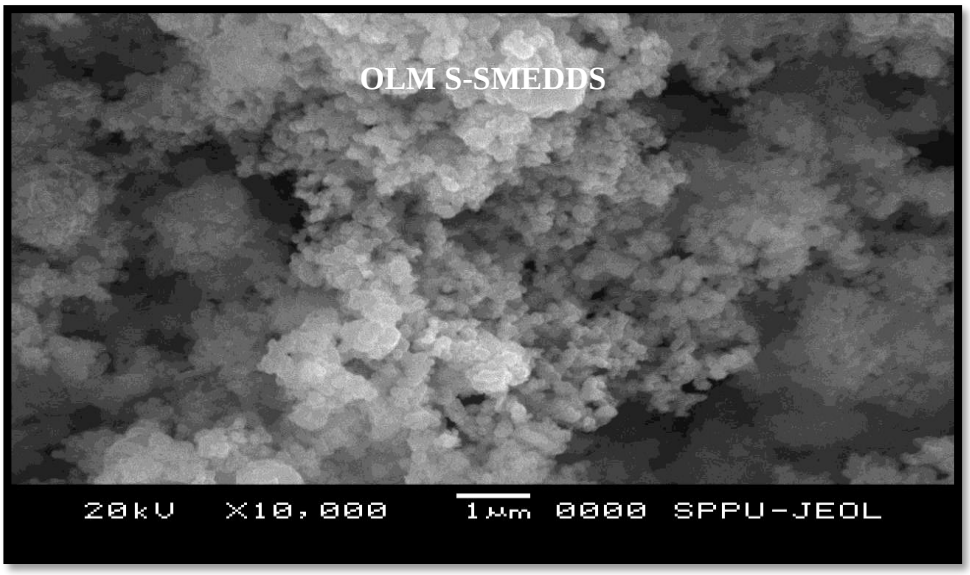


Figure 3.10 SEM of S-SMEDDS (SF6)

3.9 Stability Study

The real time stability study ($25^0C \pm 2^0C$ /60% ± 5% RH) was performed on batch SF6 for a period of three months. No significant changes were observed in appearance, Emulsification

time and Drug content. This indicated that formulation was stable at this condition. Results are shown below;

Table 3.20: Stability study data for S-SMEDDS

Evaluation Parameters	Observations			
	Initial	**30th day**	**60th day**	**90th day**
Appearance	White Amorphous Powder	No change	No change	No change
Self-emulsification time [a] (sec)	19±0.80	19.66±1.24	20±0.81	20.33±1.24
% Drug Content [a]	98.23±0.11	98.07±0.15	98.01±0.14	97.95±0.15

[a]Represents mean ± S.D. (n = 3)

CONCLUSION

Olmesartan medoxomil is orally administered novel selective angiotensin II receptor blocker for the treatment of hypertension. But its solubility and oral bioavailability are poor. The objective of our investigation was to formulate a self-micro-emulsifying drug delivery system (SMEDDS) of Olmesartan medoxomil using minimum surfactant concentration that could improve is solubility of drug without causing GI irritation. The composition of optimized formulation, consisted of Oleic acid as oil, Tween 80 as surfactant and PEG-400 as cosurfactant ,scontaining 10 mg of Olmesartan medoxomil. The formulation F6 showed drug release (98.60±0.3%), droplet size (212.91 nm). Zeta potential (-43.89 mV) and infinite dilution capability. In-vitro drug release of the F6, was highly significant. The F6 was further used for the preparation of Solid-SMEDDS(S-SMEDDS) formulations (powder). The powder was prepared via adsorption to solid carrier technique Aerosil 200 as adsorbent. The in vitro release for the S-SMEDDS was 96.70±0.3%. In conclusion, the study illustrated that adsorption to solid carrier technique could be a useful method to prepare the solid SMEDDS powder from liquid SMEDDS, which can improve aqueous Solubility and oral absorption of Olmesartan medoxomil nearly equivalent to the liquid SMEDDS, but better in the formulation stability, drug leakage, precipitation, patient compliant etc. Hence, it was concluded that Solid Self-

Micro Emulsifying drug delivery system is a good approach to enhance the solubility and dissolution property of Olmesartan medoxomil.

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CONFLICT OF INTEREST

All authors declared no conflicts of interest.

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