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Original Research Paper

DEVELOPMENT AND EVALUATION OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM OF OLMESARTAN MEDOXOMIL BY USING ADSORPTION TO SOLID CARRIER TECHNIQUES

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ABSTRACT

Olmesartan medoxomil (OLM) is an angiotensin II receptor blocker antihypertensive agent. It is a highly lipophilic (log p (octanol/water) 5.55), poorly water soluble drug with absolute bioavailability of 26%.The main objective of this study was to prepare a solid form of lipid based self emulsifying drug delivery system by adsorption to solid carrier technique to improve the oral bioavailability of poorly water soluble drug Olmesartan medoxomil. The solubility of OLM was determined in various vehicles like oils, surfactants and co-surfactants. Pseudoternary phase diagrams were constructed to identify the efficient self-emulsifying region. The liquid SEDDS was a system that consist of Olmesartan, Acrysol k-150, Labrasol, Transcutol P as a drug, oil, surfactant and co-surfactant. The optimized liquid SMEDDS was transformed into a free flowing powder using Avicel or Aerosil 200 as the adsorbent. Prepared SEDDS formulations were tested for microemulsifying properties and the resultant microemulsions were evaluated for robustness to dilution, assessment of efficiency of self emulsication, emulsification time, turbidity measurement, viscosity, drug content and in-vitro dissolution. The optimized SEDDS formulation further evaluated for heating cooling cycle, centrifugation studies and freeze thaw cycling, particle size distribution, zeta potential were carried out to confirm the stability of the formed SEDDS. The formulation was found to show a significant improvement in terms of the drug release with complete release of drug within 60 minutes 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..The dissolution of the drug was enhanced significantly from the SMEDDS formulation as compared to pure drug.

Keywords: Olmesartan medoxomil, Solid self-microemulsifying drug delivery system, Adsorption, Dissolution.

INTRODUCTION

Olmesartan medoxomil (OLM) is a non peptide, orally active is an angiotensin II receptor blocker used to treat high blood pressure. OLM is an ester-type prodrug that is esterified during and/or after its absorption in the gastrointestinal tract. OLM is poorly soluble and aqueous solubility is reported to be less than 1 mg/ml. oral administration, with a bioavailability approximately 26%. Peak plasma concentrations of OLM occur 1 to 2 h after an oral dose and are highly bound to plasma proteins (99%). Rapid onset of action is desirable to provide fast relief in the treatment of heart failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of OLM to obtain faster on set of action, minimize the variability in absorption, and improve its overall oral bioavailability. The various formulation strategies reported in the literature include the use of surfactants, cyclodextrin complexes, nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers. There has been increasing focus on the utility of lipid-

based formulations are reported to assist the absorption of poorly soluble drugs by reducing the inherent limitation of slow and incomplete dissolution. 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-emulsifying drug delivery system (SEDDS) 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 SEDDS allowing them to be encapsulated as unit dosage forms for per oral administration. 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. SEDDS 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. 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 SEDDS are able to offer the advantages of SEDDS 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 SEDDS.

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

MATERIALS AND METHODS

Materials

Olmesartan medoxomil was obtained as a generous gift from CTX Life Science, Surat, India. Acrysol k-150, & Acrysol EL-135 was Gifted sample from Corel Pharma Chem, Gota, Ahmedabad. Labrasol were gifted by Gattefosse Ltd., Mumbai, India. Transcutol p was taken from Rajesh Chemicals, Mumbai. Aerosil 200 and Avicel pH101 was taken by Ozone International, Mumbai.

Methods

Solubility Studies

Solubility studies were carried by placing an excess amount of OLM in a screw capped vials containing 2 mL 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 (milligram/mL) ± SD.

Construction of Pseudoternary Phase Diagrams

The micro emulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a micro emulsion: an oil phase, an aqueous phase and a surfactant. If a co-surfactant is used it may sometimes be represented at a fixed ratio to surfactant as a single component and treated as a single "pseudo-component. The phase behavior of simple SEDDS comprising of oil, water, surfactant mixture can be added with the aid of ternary phase diagram in which each corner of diagram represents 100% of that particular components. 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. The various surfactant/co-surfactant (Smix) 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/Smix 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-Smix 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 Smixratio. 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 SEDDS formulations were stored at ambient temperatures until further use.

Table1: Formulation of Olmesartan medoxomil liquid SEDDS

Formulation code	OLM (mg)/%	Acrysol k-150 (%)	Labraol (%)	Transcutol (%)
F1	20	20	40	20
F2	20	10	45	20
F3	20	10	30	
F4	20	20	20	
F5	20	20	10	
F6	20	10	-	40
F7	20	10	-	30

Preparation of Solid Self Emulsifying Drug Delivery System

Adsorption to solid carriers

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. 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. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w) onto suitable carriers Solid carriers such as Aerosil 200 or Avicel pH 101.Solid-SEDDS was prepared by mixing liquid SEDDS containing OLM with Aerosil 200 or Avicel pH 101 in 1:2, 1:1,as. 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.

Charaterization of SEDDS

Determination of λ max of Olmesartan medoxomil in methanol

Preparation of standard stock solution of Olmesartan medoxomil & Determination of λmax & Construction of calibration curve: Olmesartan medoxomil (100 mg) was accurately weighed and transferred to the 100 ml volumetric flask and diluted up to the mark with methanol to obtain final concentration of 1000 µg/ml and used as a stock solution. From the stock solution working standard solutions from10 µg/ml was prepared by appropriate dilution with methanol. They were scanned in the UV region of 400-200 nm. The spectrum was obtained and the maximum absorbance was found out for detection λ max of in Olmesartan medoxomil methanol. By using the above stock solution with appropriate dilutions of the 0.2, 0.4, 0.6, 0.8, 1.0 ml withdrawn in 10 ml volumetric flask and diluted to10ml methanol to produce concentration 2, 4, 6,

8, 10µg/ml respectively and absorbance of these solutions were estimated using UV spectrophotometer. Calibration graph was plotted as concentrations verses absorbance.

A Number of Tests are Carried out for Characterization of SEDDS

1. Dispersibility test

The dispersibility test of SEDDS was carried out to assess to compatibility to disperse into emulsion and the size of resulting globules to categorize them as SEDDS. It was carried by using a standard USP Paddle type dissolution test apparatus, formulation was added to 500 ml of water at 37±0.5 ^{o}C and the paddle was rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture which was of different type. Depending upon which the in vitro performance of formulation can be assessed**.**

Table 2: Type of formulation depending upon visual observation

Sr. No.	Dispersibility and apperance	Grade	Time to SE (Min)
1.	Rapidly forming (Within 1 min)Nano or microeulsion having a clear or bluish appearance	**A**	Within 1
2.	Rapidly forming, slightly clear emulsion having a bluish white appearance	**B**	Within 1
3.	Fine milky emulsion that formed within 2 min	**C**	Within 2
4.	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min)	**D**	Within 3
5.	Exhibit poor or minimal emulsification with large oil droplets presents on the surface	**E**	Within 3

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

2. Visual assessment

OLM SM was diluted with purified water (100 ml) and gently stirred with magnetic stirrer. Temperature should be 37^{0}C.

3. Determination of self-emulsification time

The emulsification time of SMEDDS was determined according to Chinese Pharmacopoeia (2005 version), dissolution apparatus. One ml of each formulation was added drop wise to 500 ml distilled water at 37±.5^{0}C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time assessed visually.

4. Rheological properties determination

The SEDDS system can also be administered in soft gelatin capsules; it should have appreciable flow properties for processing. The rheological properties (viscosity, thixotropy, flow, static yield, creep value)of the formulation (diluted to 0.5 %v/v water)are determined by rotational viscometers, digital instruments coupled with either cup and bob or coaxial measuring device. A type of rotational viscometer has also been used for determination of liquid SEDDS also indicates whether the system is o/w to, as low viscosity systems are o/w and high viscosity system are usually w/o in nature. Viscosity of formulation is inversely proportional to dilution

5. Thermodynamic stability studies

The physical stability of a lipid formulation is very important for its performance as its can be adversely affected by precipitation of drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficiency. Also the incompatibilities between formulation &shell of capsule may cause brittleness, softness, and delayed disintegration or incomplete release of drug. The following cycles was carried out for these studies.

Heating cooling cycle

The optimized SMEDDS formulations were diluted with 100 times distilled water. **S**ix cycle between coling temp. (4°C) and heating temperature (45°C) with exposure at each temperature for not less than 48 hrs. are carried. That formulation, which was stable, then was subjected to centrifugation test.

Centrifugation

In order to estimate metastable systems, the optimized SMEDDS formulations were diluted with 100 times distilled water. Which pass heating –cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

Freeze thaw cycle

This test was performed for accelerated stability testing of Nanoemulsion formulations. In this study threefreez haw cycle of formulations were exposed between temperatures 21^0C-25^0C for each temperature cycles not more than 48 hrs. For the better estimation of accelerated stability studies six such cycles should be run for each batch of formulation. The formulations which showed the maximum stability were selected for further study.

6. Cloud point measurement

Dilute the formulation 1ml with 1000 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 micro emulsion at body temperature.

7. Refractive index and percent transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index measured using Abbes refractometer. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank 21 Stability of optimized micro emulsion formulation with respect to dilution is checked by measuring Transmittance through U.V. Spectrophotometer. Transmittances of samples are measured at 650 nm and for each sample three replicate assays are performed.

Table 3: Procedure for % transmittance

Sr. No.	Test	Procedures
1.	%Transmittance	1 ml of formulation was diluted with 100 and 1000 fold water (ml) , and % transmittance was determined using uv spectrophotometer at 650 nm.

8. Absolute drug content

Liquid SEDDS and S-SEDDS containing OLM, equivalent to 20mg was diluted in suitable quantity of methanol. The sample was mixed thoroughly to dissolve drug in methanol by stirring. Drug content in the solvent extract is filtered through 0.45 um membrane filter. Drug content analyzed by suitable analytical method against the standard solvent solution of drug.

9. Turbidimetric evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of droplet after emulsification. They determine droplet size and self-emulsification time fixed quantity of self-emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate atambient temperature, and the increase in turbidity is measured using a turbidimeter 20. The time required for complete emulsification was too short it was not possible to moniter the rate of change of turbidity i.e. rate of emulsification

10. Viscosity determinations

The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. These viscosities determination conform 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 system19.

11. Electro conductivity test

This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SMEDDS the charge on an oil droplet is negative due to presence of free fatty acids. Type of micro emulsion (o/w or w/o) and the stability of the micro emulsion can be determined by electrical conductivity (σ).

12. Macroscopic evaluation

Macroscopic analysis was carried out in order to observe the homogenecity of SEDDS. Any change in colour & transparency or phase separation occurred during normal storage condition (37+2^{O}C) was observed in optimized SEDDS.

13. Differential scanning calorimetry

All DSC analyses were carried out using TA 60 WS Instrument differential scanning calorimeter. Samples of 2 mg of the individual sub such as pure OLM, liquid SEDDS, &S-SEDDS were recorded by placing sample in the aluminium pan and while an empty pan was used as reference heated. Thermogram were obtained by the DSC 60 thermal analyzer program and recorded at constant chart speed of 1 inch/min. The thermogram, transition temperature range were recorded. DSC determines any type of chemical interaction occurred or not.

14. Scanning electron microscopy

The Liquid SEDDS and S-SEDDS was analyzed by SEM for studying particle size and shape and surface structure.

15. Powder X-ray diffraction

X-rays are the electromagnetic radiations having a wavelength of about 1Å Which is approximately the size of an atom.it is used for analysis of crystalline solids of an atomic level. PXRD is a characterization technique used by material scientists working in pharmaceutical, geological, engineering, and environmental sciences areas. The advantages associated with this techniques are:Non destructive, rapid output of results, minimal sample preparation, and easy spectra interpretation. PXRD is used to assess solid state in general. In pharmaceuticals, finds its use in the following ways.

- Identification of drugs in pharmaceutical dosage forms.
- Studying solid-solid interaction and properties of different polymorphs, solvate forms and their phase transformations.
- Drug –Excipients compatibility.
- Alteration in crystallinity of materials.

16. Fourier transform-infrared spectroscopy

In this study FTIR instrument was used. FTIR spectra for the drug and the excipients of the optimized formulations were obtained. One drop of optimized formulation is mixed with KBr and used for the analysis of FTIR spectrum. Pure drug was also mixed with KBr and spectrum was obtained. Both spectra were compared for possible deviations.

17. In vitro release

The quantitative *in vitro* release test is performed in purified distilled water as dissolution medium. The test was performed using Type 2 dissolution test apparatus (Electolabs, USP standard) S-SMEDDS (Equivalents to 20 mg of dose) are placed in gelatin capsule .at 50rpm and37±0.5^{0}c temp. during the release period to compare the release profile with conventional dosage form .Sample solutions are withdrawn at

predetermined time intervals (5, 10, 15, 20, 25, 30,35, 40, 45,60 min).filtered through a 0.45µm membrane filter, dilute suitably and analyzed spectrophotometricaly. Equal amount of fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals is calculated using the Beer Lambert's equation.

18. Stability

Stability tests are much simpler and needed less frequently for coarse dispersion, where droplets sizes and phase changes must be followed. To overcome the problem of metastable formation which are not thermodynamically stable and takes long time to separate, thermodynamic stability test are recommended. Stability was carried out as per ICH guidelines

RESULTS AND DISCUSSION

Determination of λ max and Calibration Curve of Olmesartan Medxomil in Methanol

The drug exhibited an absorption maximum at 257 nm. A linear relationship between the λ max and the concentration of Olmesartan Medoxomil was established over the examined concentration range (2 – 10µg/ml). Linear regression data are given in table brlow.

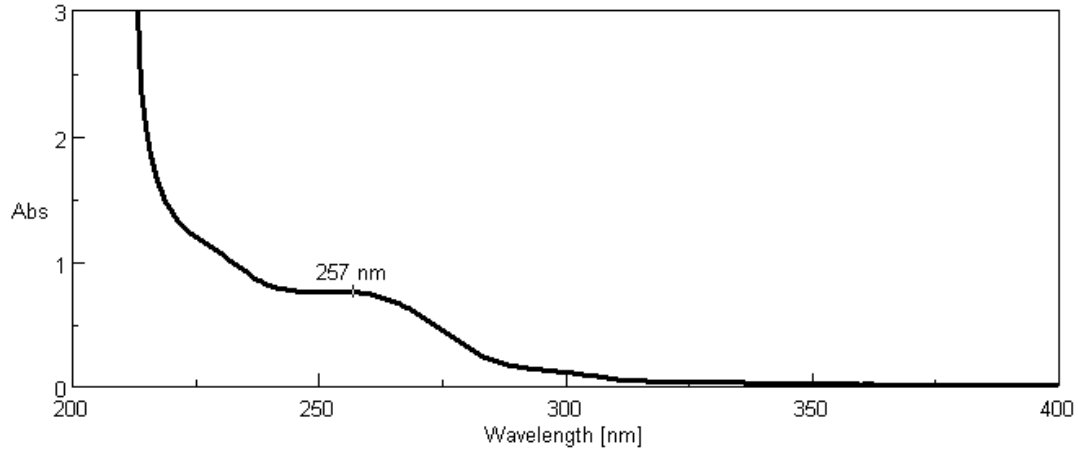


Figure1: λmax of Olmesartan medoxomilin methanol

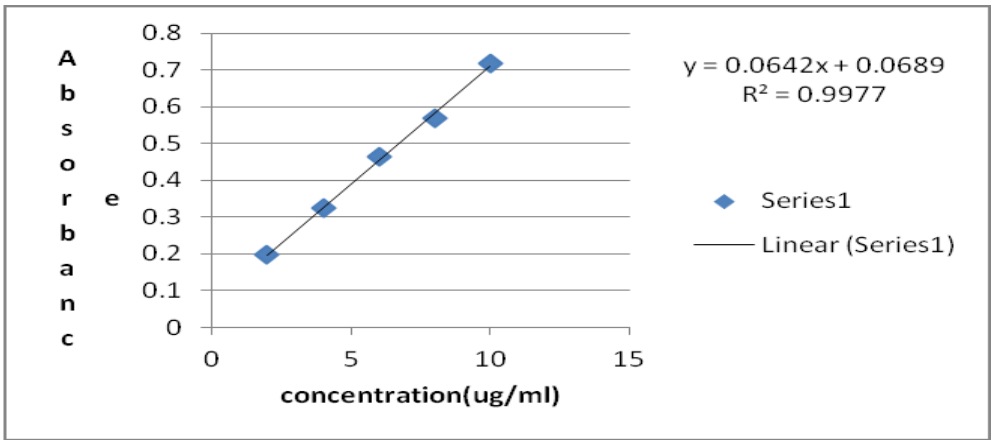


Figure 2: Linearity curve of Olmesartan medoxomil in methanol

Solubility Studies

The components in the formulation of SEDDS 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 Figure below. Solubility of Olmesartan medoxomil in various oil, surfactant, and co-surfactant in shown in figure and table.

Table no.4: Solubility of Olmesartan Medoxomil in different oil

Sr. No.	Ingredients	Solubility (mg/ml)
1	Castor oil	31.78 ± 2.36
2	Sunflower oil	45 ± 3.67
3	Acrysol k-150	71.66±0.266
4	Kardi oil	34.65 ± 1.89
5	Ground nut oil	25±1.48
6	Olive oil	26.76 ± 2.52
7.	Acrysol EL-135	68±0.567

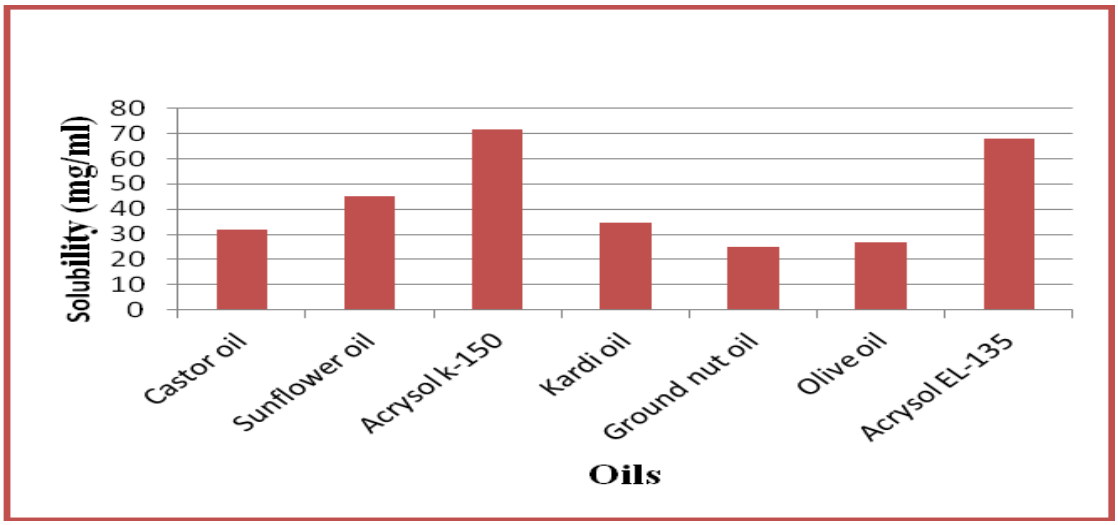


Figure 3: Solubility of Olmesartan medoxomil in different oil

Table 5: Solubility of Olmesartan medoxomil in different Surfactant

Sr. No	Ingredients	Solubility (mg/ml)
1	Labrasol	71.56 ± 27
2	Tween 80	59.90± 2.12
3	Tween 20	65.32 ± 2.88
4	SPAN 80	56 ± 27
5	SPAN 20	50.76 ± 1.23

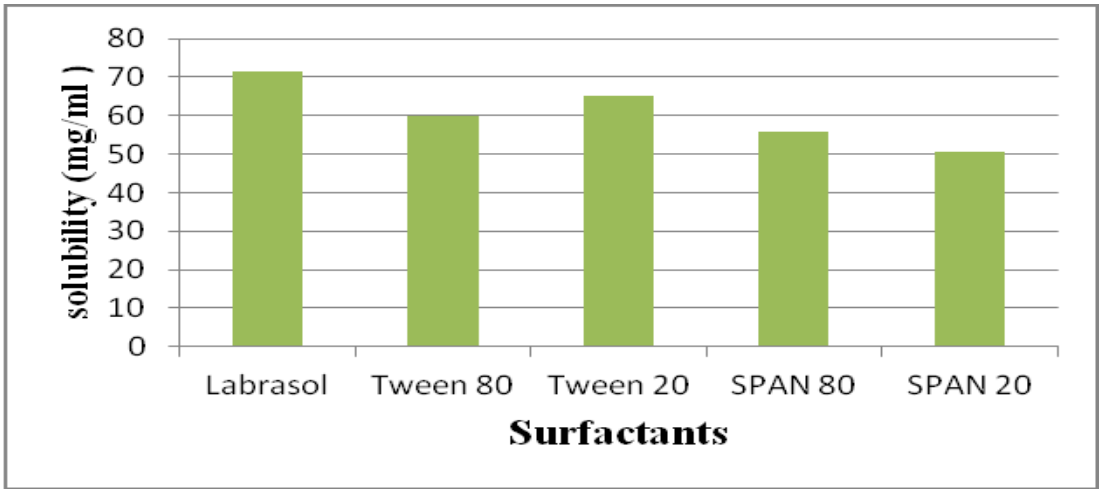


Figure 4: Solubility of Olmesartan medoxomil in different Surfactant

Table 6: Solubility of Olmesartan medoxomil in different Co- Surfactant

Sr. No	Ingredients	Solubility (mg/ml)
1	Transcutol p	130 ±5.76
2	PEG 400	65.26 ± 2.57
3	Propylene glycol	83.61 ± 2.77

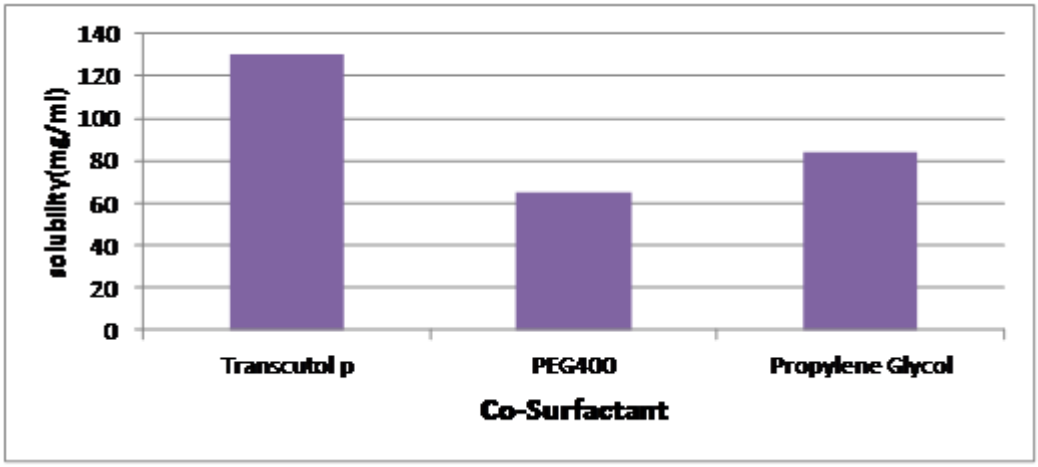
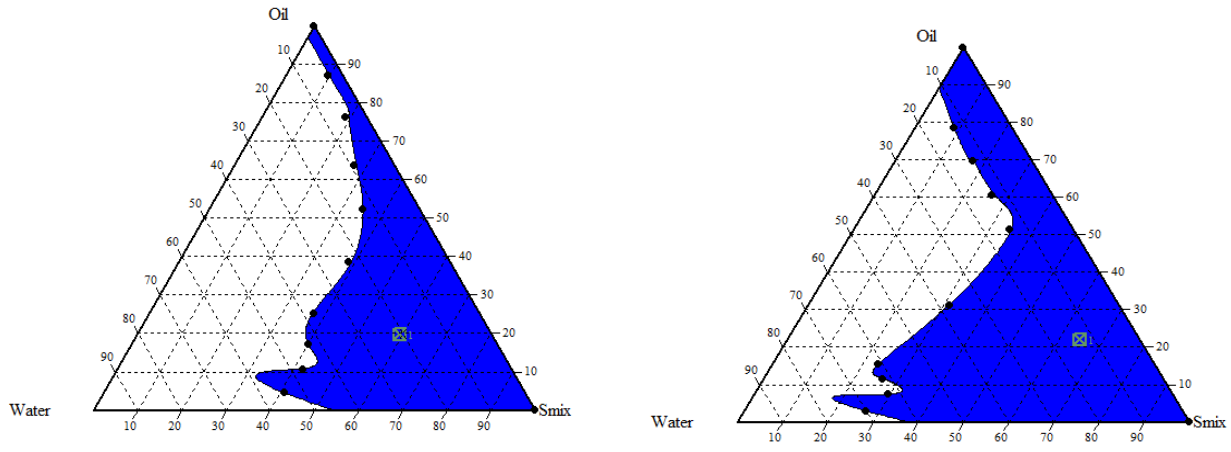


Figure 5: Solubility of Olmesartan medoxomil in different co-surfactant

In the present study, amongst the various vehicles tested, highest solubility of OLM was observed in Acrysol k-150. Thus the same was chosen as the oily carrier phase for formulating the SEDDS system. Amongst the surfactants screened Labrasol and Transcutol p were found to possess good solubilization potential for OLM and were chosen as the surfactant mixture to formulate the SEDDS.

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



(a) **(b)**

Figure 6: (a) Pseudoternary phase diagrams involving oil: (smix) and water with ratio of 1:2.
(b) Pseudoternary phase diagrams involving oil: (smix) and water with ratio of 2:1

Dispersibility Test

The Liquid SEDDS was evaluated for dispersibility test as given in experimental work and studies the various formulation shows the following results in shown tables below.

Self-emulsification Time-Emulsification time

This was observed gives in table below.

Table 7: Type of formulation depending upon visual observation and self-emulsification time

Sr. No.	Dispersibility and Apperance	Grade	Time in SE(Min)
F1	Dull	C	Within 2
F2	Clear	A	Within5
F3	Transperant	B	Within1
F4	Clear and Transperant	A	Within1
F5	Dull	C	Within 2
F6	Clear and Transperant	A	Within 1
F7	Clear	A	Within1

Viscosity Determination

Table 8: Viscosity of SEDDS formulations

Sr. No.	Formulation code	Viscosity at rpm (cps)
1	F1	24.87± 0.28
2	F2	21.84 ± 0.56
3	F3	45.75 ± 0.45
4	F4	29.04 ± 0.53
5	F5	32.65 ± 0.27
6	F6	19.74± 0.65
7	F7	27.88± 0.43

Thermodynamic Stability Studies

Table 9: Screening of formulations on the basis of thermodynamic stability studies

Sr. No.	Batch code	Observation based on thermodynamic stability studies		
		Freeze throw cycle	Heating/Cooling cycle	Centrifugation
1	F1	×	×	×
2	F2	×	√	√
3	F3	√	×	√
4	F4	√	×	×
5	F5	√	√	√
6	F6	√	√	√
7	F7	√	√	×

% Transmittance and Clouding Point Determination

Table 10: % Transmittance and Clouding point of formulation

Sr. No.	Formulation code	% Transmittance	Clouding point (^{0}c)
1	F1	98.5±0.026	80
2	F2	87.32±0.012	75
3.	F3	96±0.058	78
4.	F4	97.78±0.054	82
5.	F5	99.87±0.013	84
6.	F6	97.12±0.043	82
7.	F7	98.64±0.056	81

Drug Content of SMEDDS

The percent drug content of all the SEDDS formulation were found be in the range of 95.32±0.056 to 97.88±0.0305%. They showed the drug uniformly distributed in the formulation.

Table 11: Drug content of all the formulations

Sr. No	Formulation code	% drug content
1	F1	96.97 ±0.02946
2	F2	95.15 ±0.03256
3	F3	94.72 ±0.04956
4	F4	97.64 ±0.02374
5	F5	98.29 ±0.02100
6	F6	95.94 ±0.04258
7	F7	94.42 ±0.03201

The drugs content of F5 formulation was found to be 98.29% while other formulation drug content found less than 97% so it was concluded that F5 formulation have more drug content as compare to others.

Turbidimetric Evaluation

Table 12: Turbidity measurement of all the formulations

Sr. No.	Formulation code	Turbidity (NTU)
1	F1	0.018
2	F2	0.023
3	F3	0.005
4	F4	0.015
5	F5	0.004
6	F6	0.017
7	F7	0.012

Zeta Potential Determination

Table 13: Zeta potential of formulations

Sr. No.	Formulation code	Zeta potential (Mv)
1	F1	-2.87
2	F2	-6.88
3	F3	-1.45
4	F4	-3.9
5	F5	-4.31
6	F6	-6.95
7	F7	-3.5

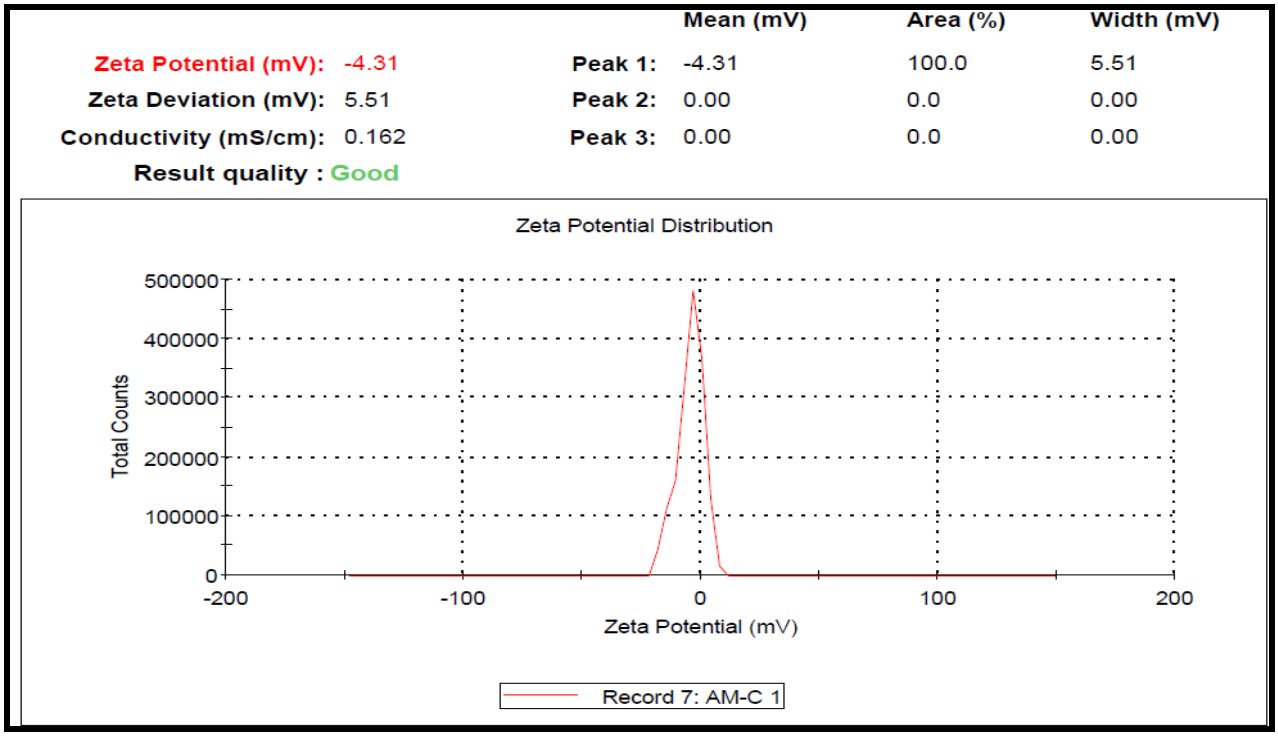


Figure 7: Zeta potential of optimized batch F5

Refractive Index

Refractive index of all formulations shown in following table

Table 14: Refractive index of all formulations

Sr. No.	Batch code	Refractive Index
1	F1	1.361
2	F2	1.350
3	F3	1.299
4	F4	1.331
5	F5	1.333
6	F6	1.330
7	F7	1.331

Electroconductivity Test

Table 15: Electro Conductivity of SMEDDS formulations

Sr. No.	Batch code	Conductivity study (mS/cm)
1	F1	0.160±0.015
2	F2	0.156±0.002
3	F3	0.170±0.010
4	F4	0.181±0.011
5	F5	0.184±0.016
6	F6	0.168±0.010
7	F7	0.172±0.011

Differential Scanning Calorimetry

The DSC thermogram of pure Olmesartan medoxomil showed the endothermic peak at 178^{0}C indicated the melting point whereas liquid SEDDS showed the peak at 202^{0}C and the adsorption to solid carrier formulation (F5) shows the peak at 198^{0}C. There was no sharp change in melting point of drug. Thus there was no significant interaction between the drug, surfactant and polymer See figure below.

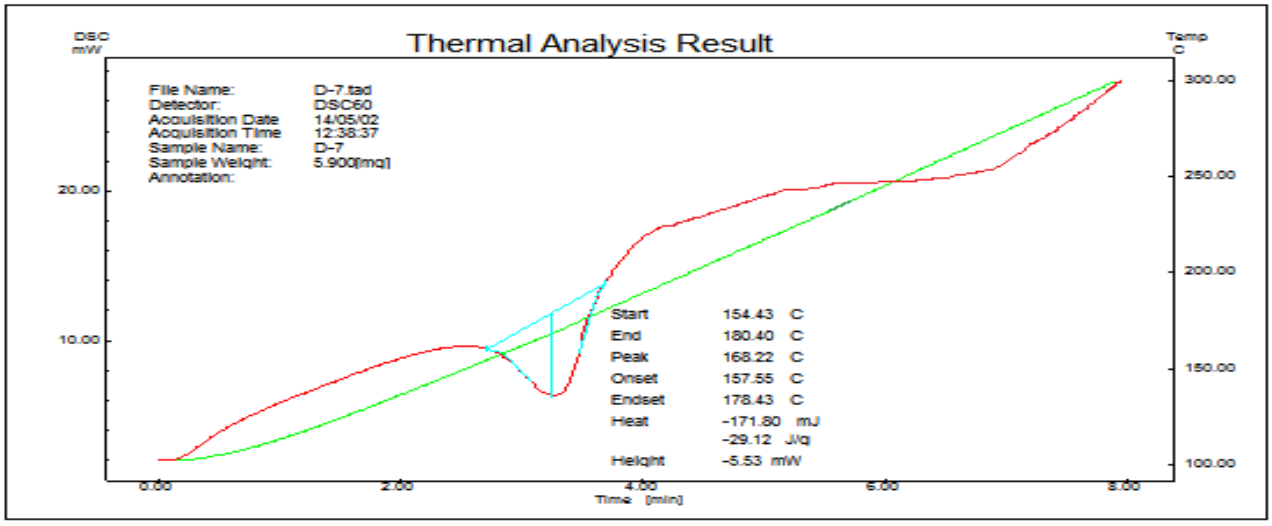


Figure 8: DSC Spectra of Olmesartan medoxomil

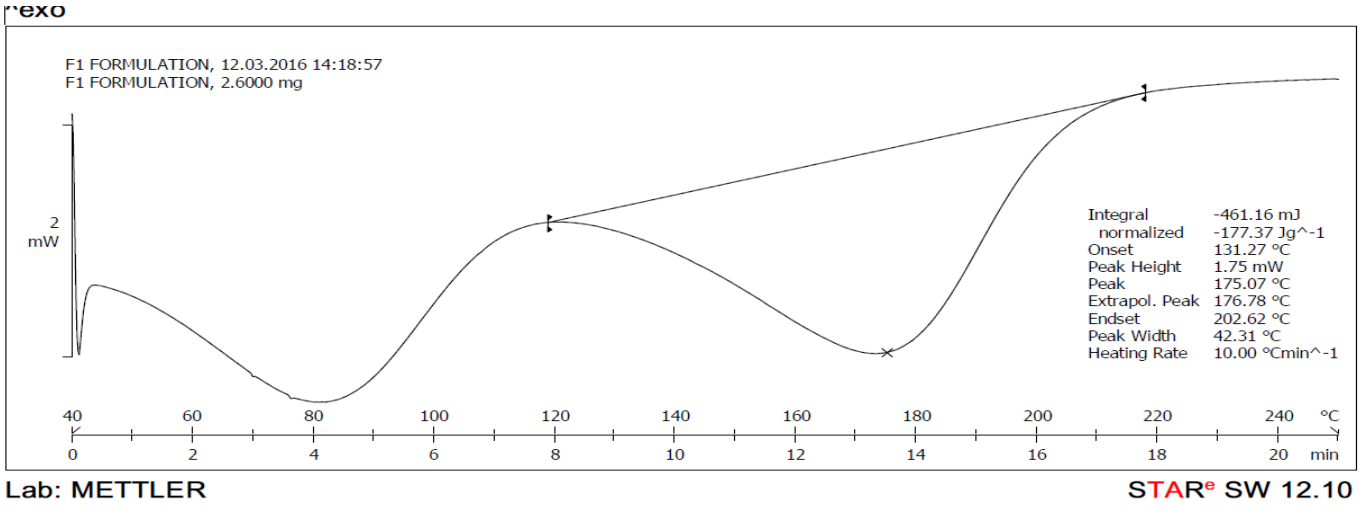


Figure 9: DSC Spectra of liquid SEDDS

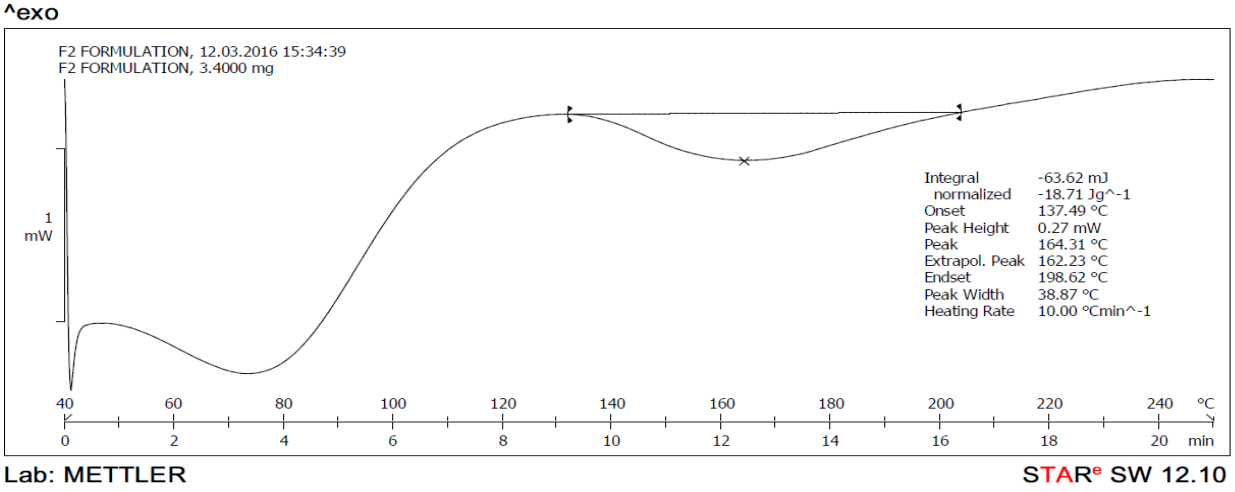


Figure 10: DSC Spectra of S-SEDDS

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) is widely used to visualize the surface topography and chemical composition of material of various types. The formulation F5 was analysed by SEM for studying particle shape and surface for pure and S-SEDDS. The shape of formulation is spherical, rod and surface is somewhat smooth in figures.

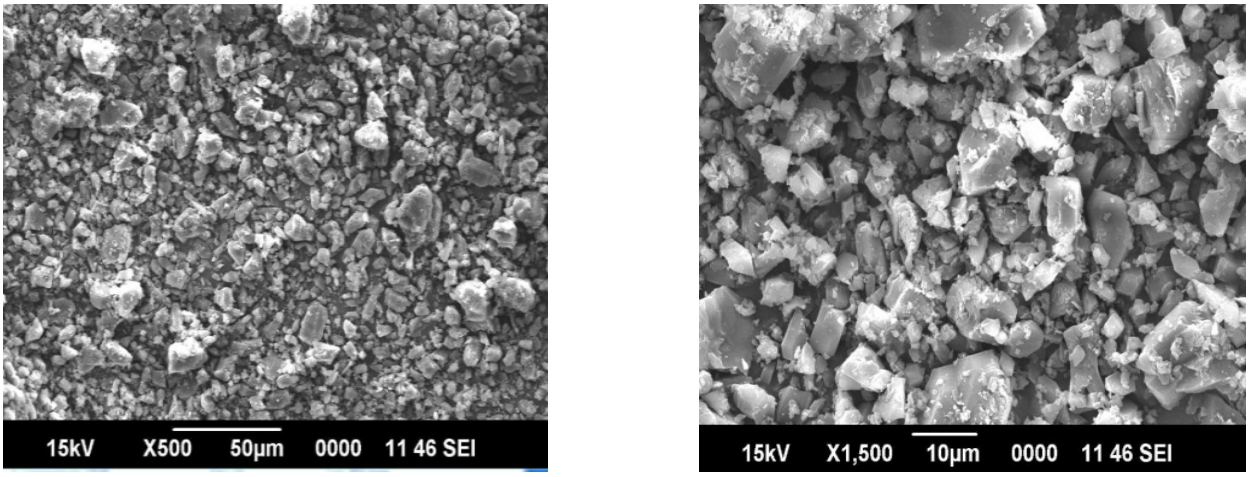


Figure 11: Scanning Electron Microscopy of Liquid SEDDS

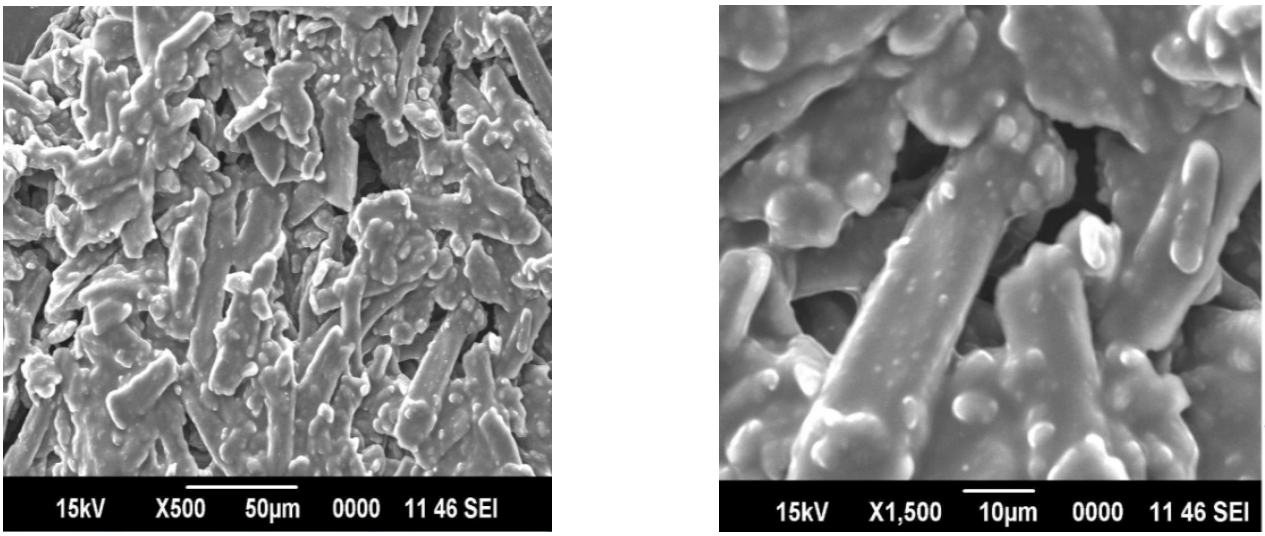


Figure12: Scanning Electron Microscopy of Solid SEDDS

FT-IR SPECTROSCOPY

Drug- Excipients Compatibility Studies

Fourier transformed infrared (FTIR) spectra was taken by using the KBr disk method. The scanning range was 400 to 4000 cm^{-1} and resolution was 1cm $^{-1}$. The major peaks in recorded spectra were compared with standard spectra given in figure below. So it can be concluded that the spectra of pure drug Olmesartan medoxomil and the combination of drug with additives, it was observed that all the characteristic peaks of Olmesartan medoxomil were present in the combination spectrum, thus indicating compatibility of the drug and additives.

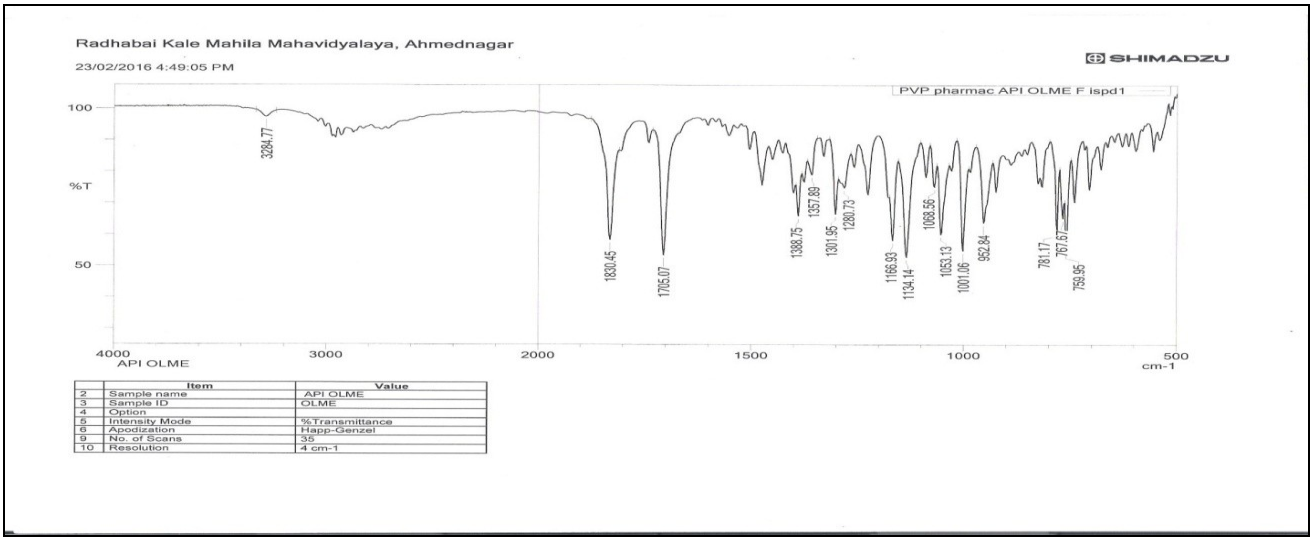


Figure13: FT-IR Spectra of Olmesartan medoxomil

Table 16: FT-IR Spectra range for Olmesartan medoxomil

Sr. No.	Compound	Functional group	Frequency(cm^{-1})
1.	Olmesartan medoxomil	3284.77	Aromatic 3^0 amine N-H Stretch
		1357.89	C – N (Aromatic 3^0 amine C-N stretch)
		3401	Aromatic 2^0 amine N-H Stretch
		1388	C – N(Aromatic 2^0 amine C-N stretch)
		1705	C=O Stretch
		1134.14	C-O-C

Fourier transformed infrared (FTIR) spectra of Olmesartan medoxomil was taken by using the KBr disk method. The scanning range was 400 to 4000 cm^{-1}. The major peaks in recorded spectra were compared with standard spectra given in figure below. So it can be concluded that Olmesartan medoxomil was identified.

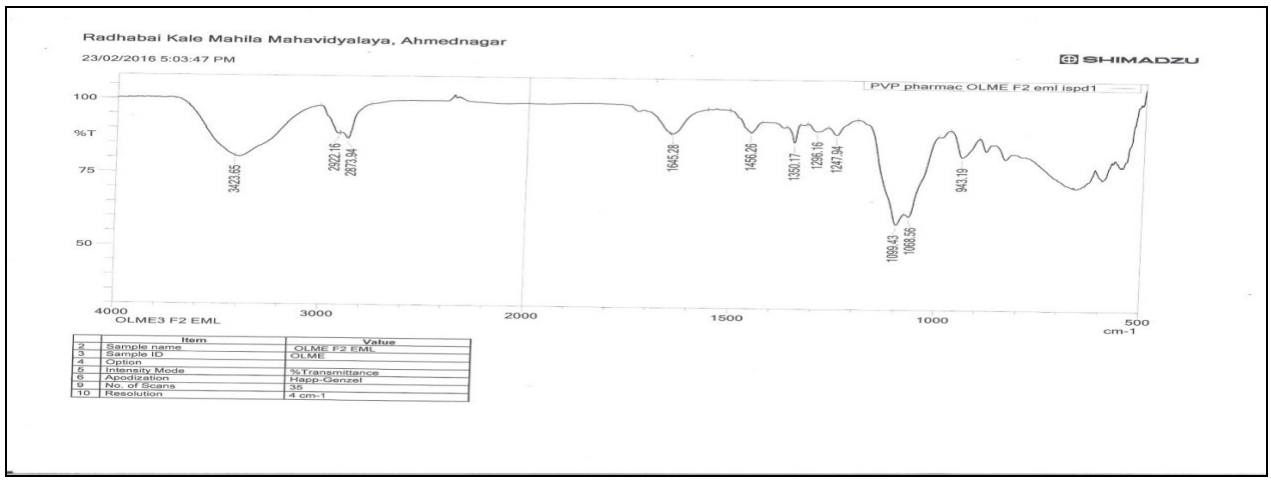


Figure 14: FT-IR Spectra for liquid SEDDS

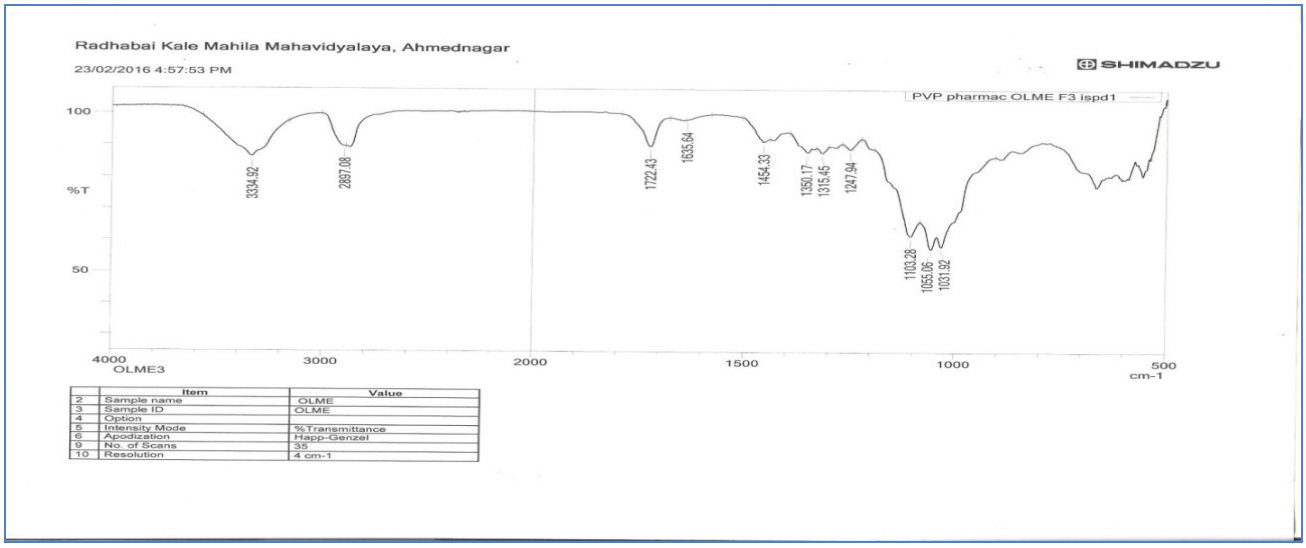


Figure 15: FT-IR Spectra of S- SEEDS of Olmesartan medoxomil (Drug+oil+S_{mix} + Solidifier)

Table 17: FT-IR Spectra range for Liquid SEDDS

Sr. No	Compound	Functional group	Frequency(cm^{-1})
1	Emulsion	3423.65	Aromatic 3^0 amine N-H Stretch
		1350.17	C – N (Aromatic 3^0 amine C-N stretch)
		3401	Aromatic 2^0 amine N-H Stretch
		1456.26	C – N(Aromatic 2^0 amine C-N stretch)
		1645.28	C=OStretch
		1099.43	C-O-C

Table 18: FT-IR Spectra range for Solid-SEDDS

Sr. No.	Compound	Functional group	Frequency(cm^{-1})
1.	S-SEDDS	3334.92	Aromatic 3^0 amine N-H Stretch
		1350.17	C – N (Aromatic 3^0 amine C-N stretch)
		2897.08	Aromatic 2^0 amine N-H Stretch
		1454.64	C – N(Aromatic 2^0 amine C-N stretch)
		1635.64	C=O Stretch
		1103.28	C-O-C

X-Ray Diffraction

X-ray Diffraction of spectra of Olmesartan medoxomil has sharp at different diffraction angle, which showed typical crystalline pattern. Olmesartan medoxomil adsorption technique shows peaks of low intensity indicating that some amount of drug converted into amorphous form.

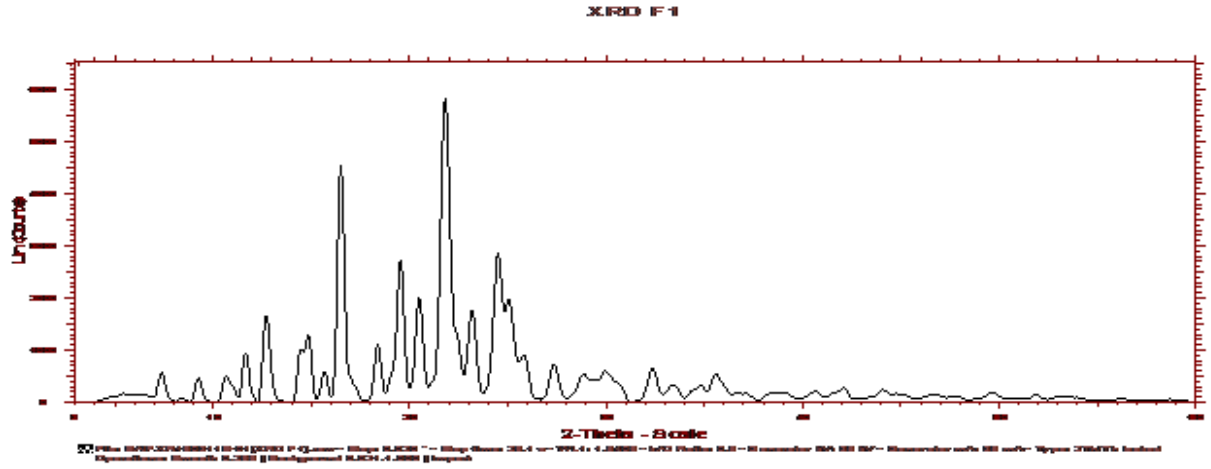


Figure 16: XRD of Liquid SEDDS

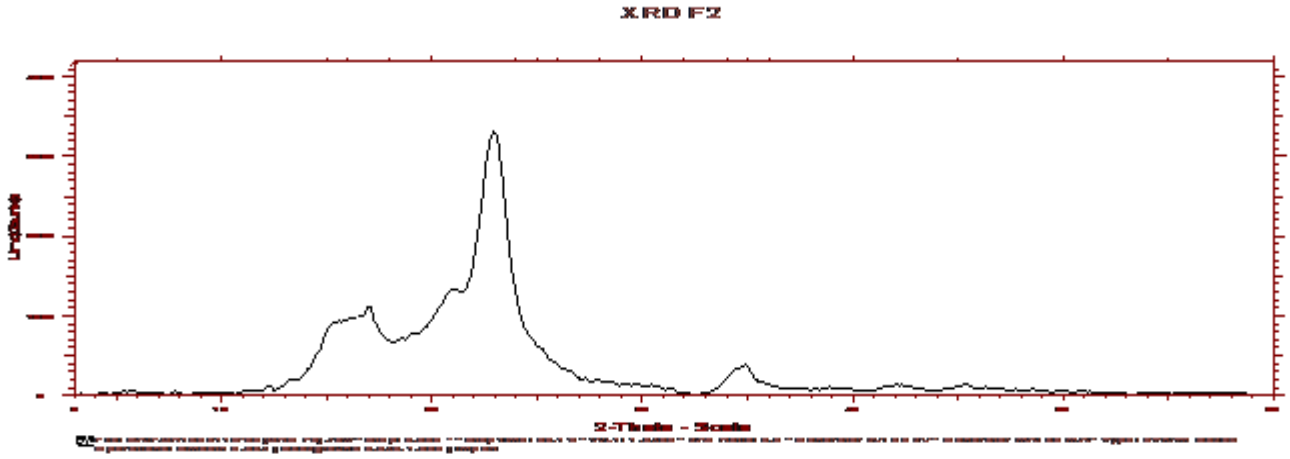


Figure 17: XRD OF S-SEDDS

The *In-Vitro* Dissolution Study

The SEDDS and plain OLM were carried out using USP- type-II dissolution test apparatus in 900 ml of Phosphate buffer pH 6.8 solutions at 37 ± 2^0C with 50 rpm rotating speed. Samples of 1 ml were withdrawn at regular time interval of 5, 10, 15, 30, 45 and 60 min. and filtered using 0.45 µm filters. An equal volume of respective dissolution medium was added to maintain the volume constant. Drug content from sample was analyzed using UV-spectrophotometer at 257.0 nm. All measurements were done in triplicate from three independent samples.

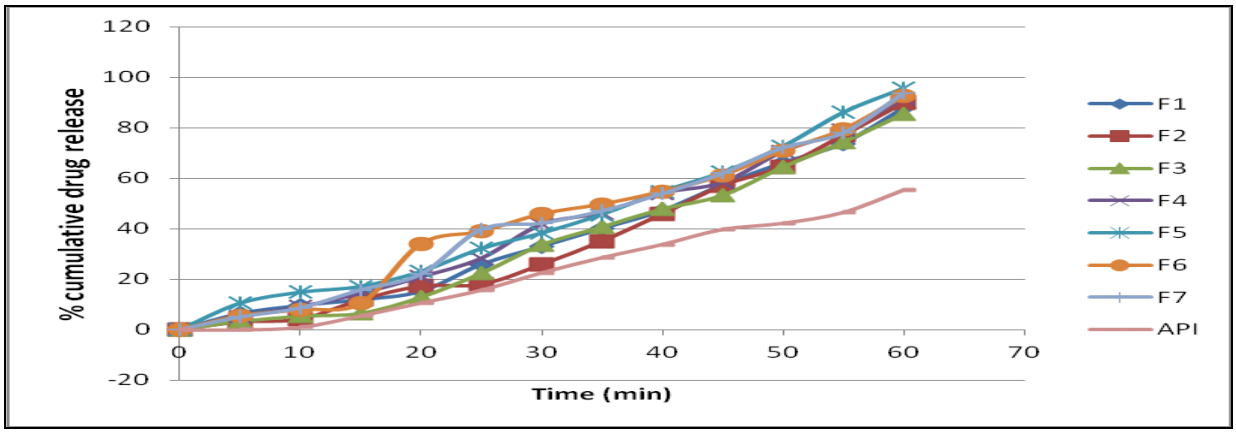


Figure 18: *In- vitro* dissolution study of SEDDS &API formulation

Stability

From the stability study, it was found that the evaluated formulation (F5) Showed there was no influence of verity of environment factors such as temperature, humidity and light, and during storage conditions or shelf life of drug in table below.

Table 19: Stability study data of optimized batch F5

Physical Parameter	Observations		
	30^{th} day	60^{th} day	90^{th} day
% Drug content	98.75	98.23	98.10

CONCLUSION

In the current investigations SEDDS of Olmesartan was prepared and evaluated for various parameters. The optimized liquid SEDDS, F5 was successfully transformed into a free flowing powder using Avicel pH 101 without affecting the self-micro emulsifying ability of the liquid SEDDS. 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-SEDDS is an indication of improvement in solubility, dissolution rate and bioavailability of the drug.

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