Preparation and Evaluation of Solid-Self-Emulsifying Drug Delivery System Containing Olmesartan Medoxomil by using Capmul MCM-E8, Tween-80 and PEG 200

* Miss. Pranali Kumbhalkar [1], Mr. Aslam Riyaz [2], Mrs. Swati V Bodhankar [3],

Mr. Lokesh Mahajan [4], Mr. Deepraj Tayade[5]

[*1] Assistant Professor, Dept. of Pharmaceutical Chemistry, Central India College of Pharmacy, Nagpur.

[2] Assistant Professor, AMCES Institute of Pharmacy, Lonara. Nagpur

[3, 4] Assistant Professor, Central India College of Pharmacy, Lonara. Nagpur.

[5] Gurunanak College of Pharmacy, Nagpur.

ABSTRACT:

Solubility of orally administered drug is major challenge of pharmaceutical industry as nearly 35-40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality. This can be increased by different methods like salt formation, solid dispersion and complex formation. Self-Emulsifying Drug Delivery System is gaining popularity for improving the solubility of lipophilic drugs. SEDDS are defined as isotropic mixtures of one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. Present review provides an updated account of advancements in SEDDS with regard to its composition, evaluation, different dosage forms and newer techniques to convert liquid SEDDS to solid and also various applications.

SEDDS which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil−in−water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation−related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability.

A. INTRODUCTION:

Self-emulsifying drug delivery systems are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or micro-emulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro-emulsions with a droplet size of less than 50 nm**.**

These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. When compared with emulsions, which are sensitive and meta-stable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture.

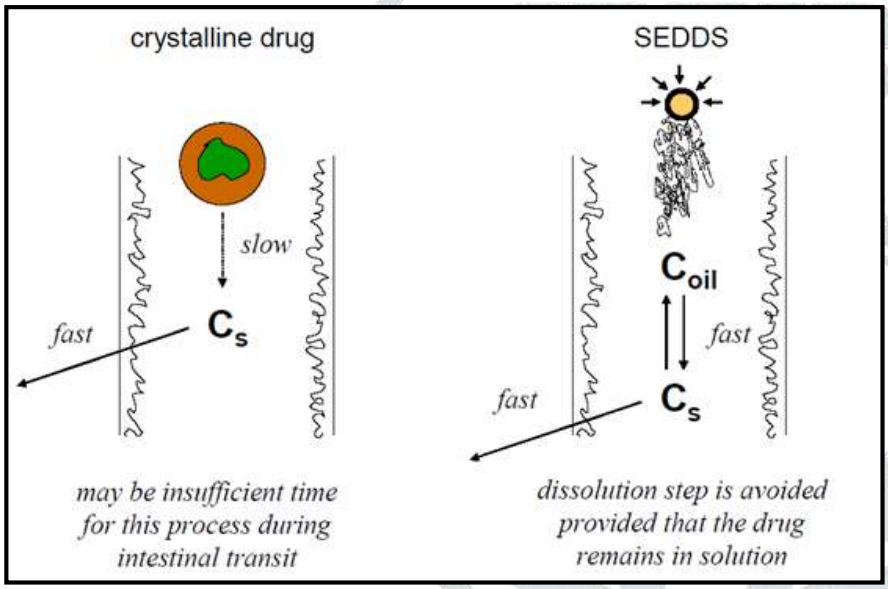


Fig. 1 Comparison study of drug partitioning in crystalline drug and SEDDS

(I) ADVANTAGES OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS.

- Emulsions are sensitive and metastable dispersed forms, whereas S-(M) EDDS are physically stable formulations that are easy to manufacture.
- Fine oil droplets of these SEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
- While compare with oily solutions, these SEDDS are afford a large interfacial area for partitioning of the drug between oil and water.
- Probable advantages of these systems include improved oral bioavailability, more consistent temporal profiles of drug absorption.

- Consequently, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.
- Enhanced oral bioavailability enabling reduction in dose.
- Control of delivery profiles.
- Reduced variability including food effects.
- High drug payloads.
- Liquid or solid dosage forms.

(II) MECHANISM OF SELF-EMULSIFICATION

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favors dispersion. Self-emulsifying process is related to the free energy. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases.

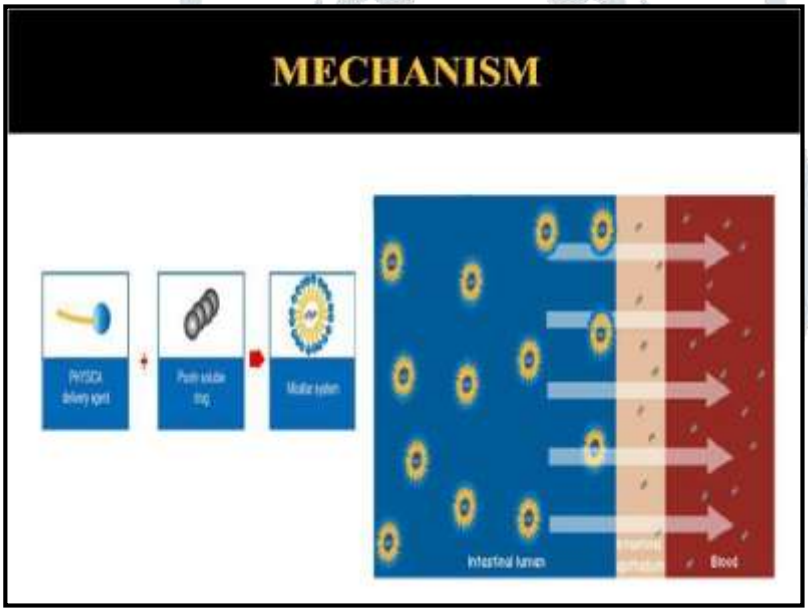


Fig. 2 Characterization of Self-Emulsifying Drug Delivery Systems

(III)METHOD OF FORMULATION OF SEDDS

The formulation of a self-emulsifying drug delivery system with a view for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self-emulsifying excipient includes various steps as described below:

- Preparation of phase diagram.

- Poorly water-soluble drug and/or pharmaceutical ingredient is solubilized in a mixture of surfactant, co-surfactant and solvent. The oil phase prepared is mixed with the solubilized drug formulation and if necessary, by heating or other preparatory means.
- The emulsion thus obtained can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

B. MATERIALS AND EQUIPMENTS

Table: 1.The list of materials used for the experimental and their manufacturer/ supplier

Sr. No.	Name of chemicals	Manufacturer / Supplier
Drug	Olmesartan Medoxomil	Ajanta Pharmaceuticals
OILS		
1	Acconon	Loba Chemicals
2	Labrafil M 1944 CS	Gattefosse India Pvt. Ltd
3	Capmul MCM – E8	Abitec Corporation
4	Castor oil	Loba Chemicals
5	Captex 200-p	Abitec Corporation
SURFACTANTS		
6	Tween 80	Loba Chemicals
7	Tween 20	Loba Chemicals
8	Triton X-100	Loba Chemicals
9	Labrasol	Loba Chemicals
CO-SOLVENTS		
10	Transcutol HP	Gattefosse India Pvt. Ltd.
11	Propylene glycol	Gattefosse India Pvt. Ltd.
12	Polyethylene glycol (PEG)- 400	Phoenix Chemicals, Inc.
13	Polyethylene glycol (PEG)- 200	Phoenix Chemicals, Inc.
ADSORBENT		
14	Aluminium Magnesium Metasilicate	Tomita Pharmaceutical Co., Lid.
OTHER EXCIPIENTS		
15	Methanol	Fisher Scientific, Mumbai
16	Sodium hydroxide	Fisher Scientific, Mumbai
17	Hydrochloric acid (Hcl)	Fisher Scientific, Mumbai
18	Disodium hydrogen phosphate	Loba Chemicals
19	Sodium dihydrogen phosphate	Fisher Scientific, Mumbai

20	Sodium chloride	Loba Chemicals

Organoleptic Properties of drug: About 1 g of drug sample was placed in watch glass and was experiential for appearance, color, any peculiar odor and taste. The melting point of the drug sample was determined by capillary method. Capillary filled with drug was placed in the melting point apparatus (Thieles tube) containing liquid paraffin as a heating medium and the melting point was noted. Reading was recorded in triplicate and the mean value was determined.

Table: 2 Characterization of Olmesartan Medoxomil

Sr. No	Characterization	Reported	Observed
1	**Organoleptic properties**	White amorphous powder with metallic odor and taste	white in color with Metallic odor and taste
2	**Melting point**	175°C - 185°C	177°C – 179.5°C

C. SPECRTOSCOPY METHODS.

1. Determination of λ_{max}: λ_{max} determination was carried out by preparing 10 µg/ml solution of Olmesartan Medoxomil in methanol and phosphate buffer (pH6.8) separately and scanned in UV range of 200-400 nm and spectrum was obtained. The λ_{max} was found to be at 256 nm wavelength as absorbance was maximum at this wavelength.

a. λ_{max} determination in Methanol

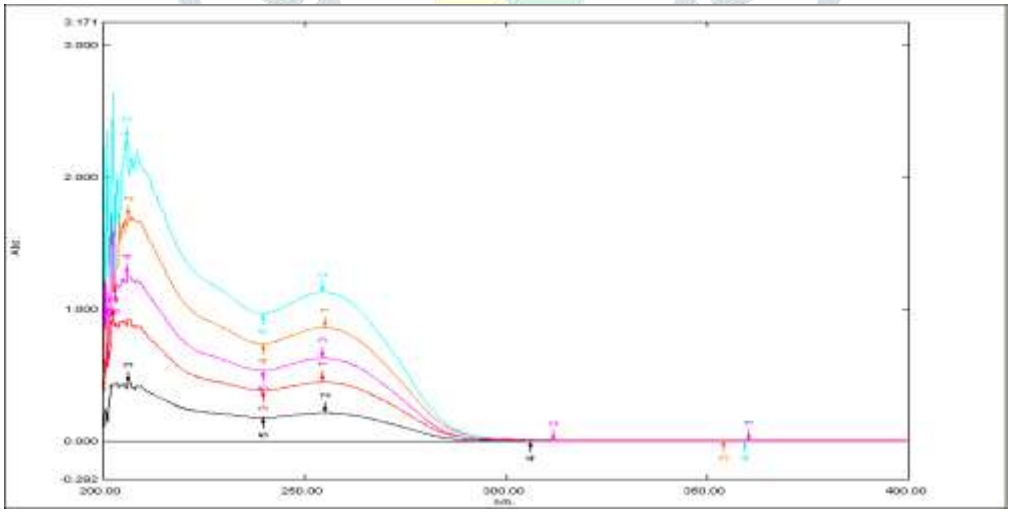


Fig. 3 UV spectrum of Olmesartan Medoxomil in methanol

2. Preparation of standard calibration curve. Accurately weighed (100mg) quantity of the drug was dissolved in methanol and phosphate buffer (pH6.8) separately and the volume was make up 100ml with the respective solvents the stock solution (1000µg/ml) were diluted with the respective solvents to give rise the series of solution containing the concentration of drug in the ranging from 10-25 µg/ml. Absorbance of these

solution was measured at 256 nm wavelength using UV visible spectrophotometer, calibration curve was obtained by plotting graph between concentration and absorbance.

Table: 3 Data of calibration curve of Olmesartan Medoxomil in methanol

Sr no.	Concentration (ug/ml)	Absorbance Standard mean deviation (n=3)
1	0	0
2	5	0.332±0.022
3	10	0.513±0.037
4	15	0.742±0.014
5	20	1.011±0.03
6	25	1.343±0.087

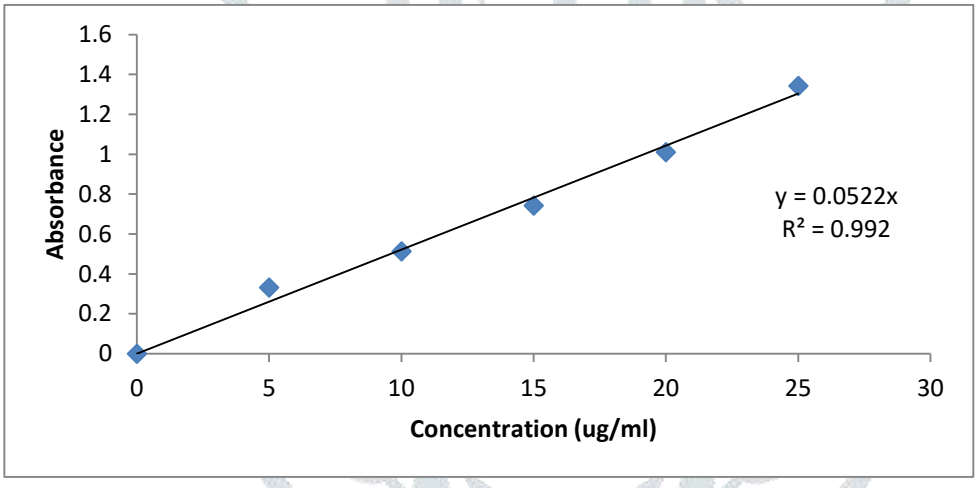


Fig. 4 Standard calibration curve of Olmesartan Medoxomil in methanol (Mean ±SD, n=3).

Table: 4 Data of calibration curve of Olmesartan Medoxomil in pH 6.8 phosphate buffer

Sr. no.	Concentration (ug/ml)	Absorbance Standard mean deviation (n=3)
1	0	0
2	5	0.225±0.032
3	10	0.476±0.027
4	15	0.696±0.054
5	20	0.894±0.013
6	25	1.145±0.027

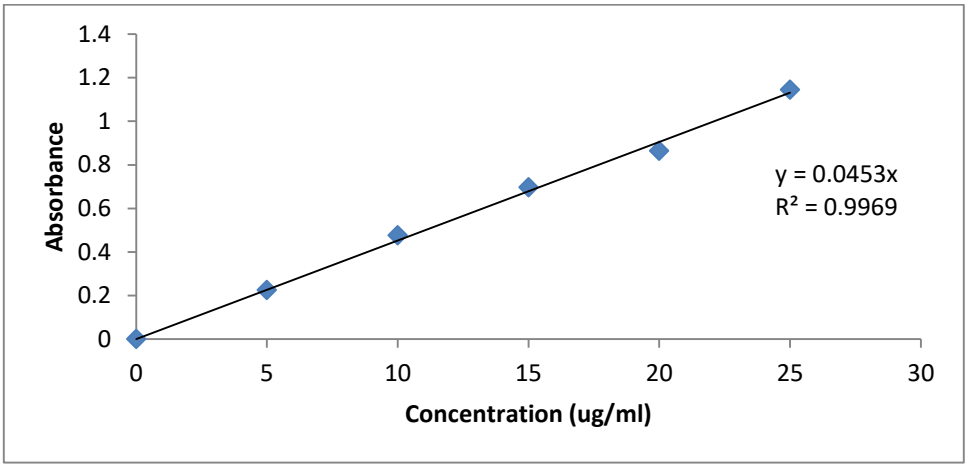


Fig. 5 Standard calibration curve of Olmesartan Medoxomil in 6.8 phosphate buffer

3. Infrared spectroscopy.

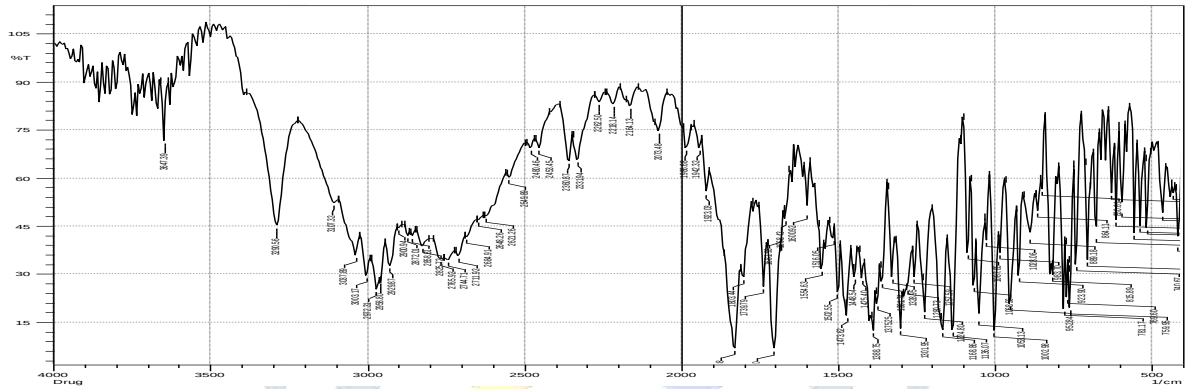


Fig.6 FTIR graph of Olmesartan Medoxomil

Table: 5 Infrared spectroscopy of Olmesartan Medoxomil

Sr. No.	Functional groups	Reported value	Observed peaks
1	Aromatic C-H stretching	3100-3000cm^{-1}	3039cm $^{-1}$
2	Aliphatic C-H stretching	3000-2850cm^{-1}	2974cm^{-1}
3	C-N stretching	1335-1250cm^{-1}	1323 cm $^{-1}$

IR spectrum indicated characteristic peaks belonging to major functional groups.

4. Scanning Electron Microscopy (SEM)

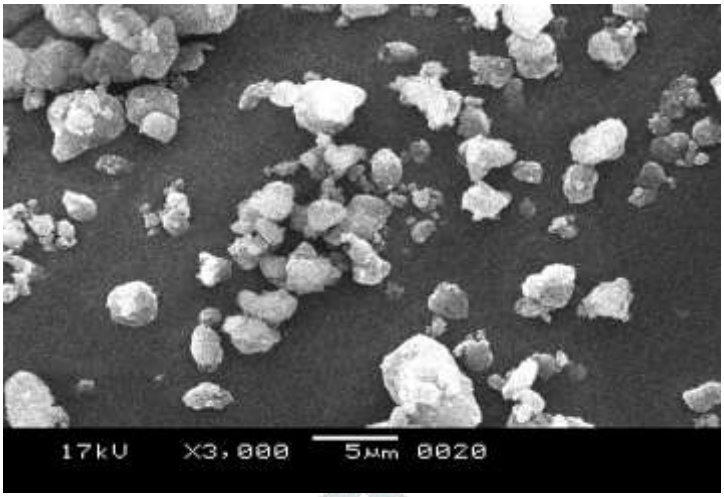


Fig.7 scanning electron Micrograph of Olmesartan Medoxomil

The sample was found to exhibit large aggregates showed in scanning electron micrograph.

5. Differential Scanning calorimetry (DSC)

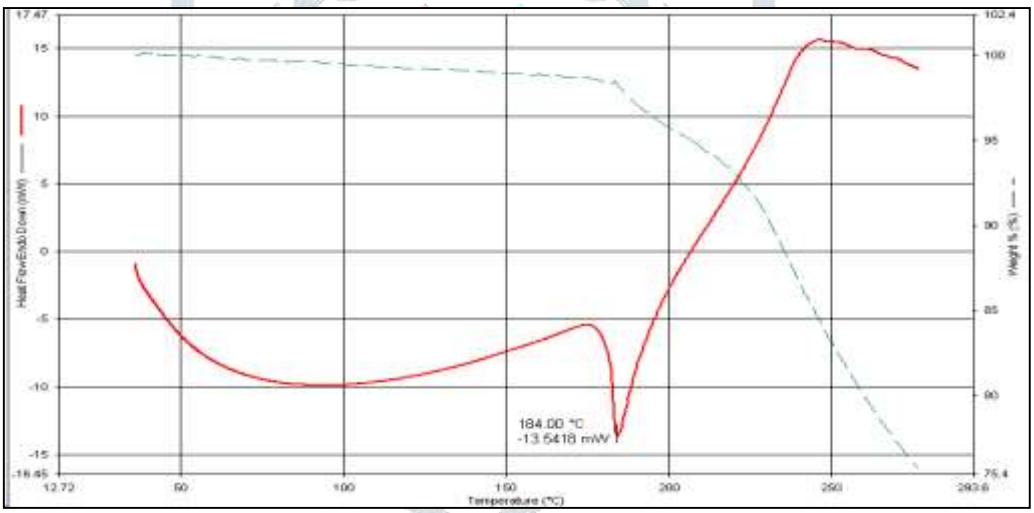


Fig. 8 DSC Curve of Olmesartan Medoxomil

Thermo gram of Olmesartan Medoxomil indicated sharp endothermic peak.

6. X-ray diffraction

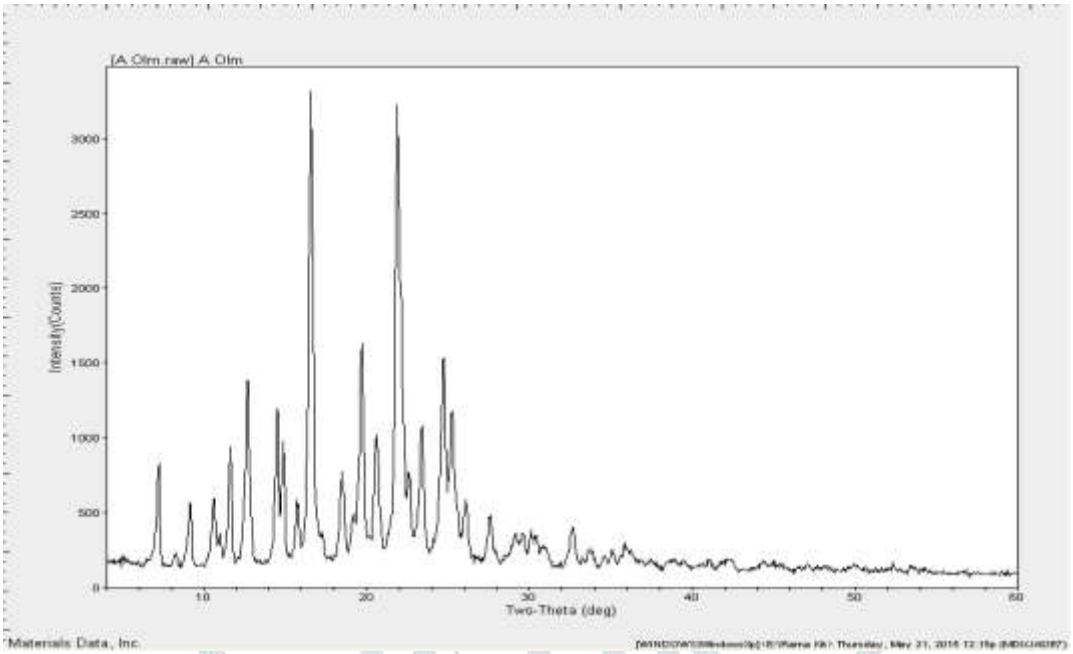


Fig. 9 X-ray diffract gram of Olmesartan Medoxomil

The Olmesartan Medoxomil drug represented numerous intense and sharp peaks.

Table: 6 Composition of SEDDS formulations

Composition Ingredients (%w/w)	OSF1	OSF2	OSF3	OSF4	OSF5	OSF6	OSF7	OSF8	OSF9
Oil	90	80	70	60	50	40	30	20	10
S(mix)	10	20	30	40	50	60	70	80	90
Ratio	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2

6.7: Evaluation of Liquid SEDDS of Olmesartan Medoxomil

7. Thermodynamic stability studies

Table: 7 Thermodynamics stability studies

Formulation code	Heating cooling cycle 4^0C /45^0C	Centrifugation	Freeze thaw cycle	Inference
OSF 1	Y	Y	Y	Passed
OSF 2	Y	Y	Y	Passed

OSF 3	Y	N	-	Failed
OSF 4	Y	Y	Y	Passed
OSF 5	Y	Y	Y	Passed
OSF 6	Y	Y	Y	Passed
OSF 7	Y	N	-	Failed
OSF 8	Y	N	-	Failed
OSF 9	Y	N	-	Failed

Y: denotes maintenance of homogeneity of prepared micro-emulsion.

N: denotes separation of components of micro-emulsion.

Amongst 9 formulations OSF 1, OSF 2, OSF 4, OSF 5 and OSF 6 passes the test.

8. Determination of Globule Size, Poly-dispersity Index

Aliquots (1ml) of the sample, serially diluted 100 fold with purified water, were employed to assess the globule size and poly-dispersity index was determined by dynamic light scattering technique using particle size analyzer (Malvern, Worcestershire, UK). [72]

9. Zeta Potential Determination

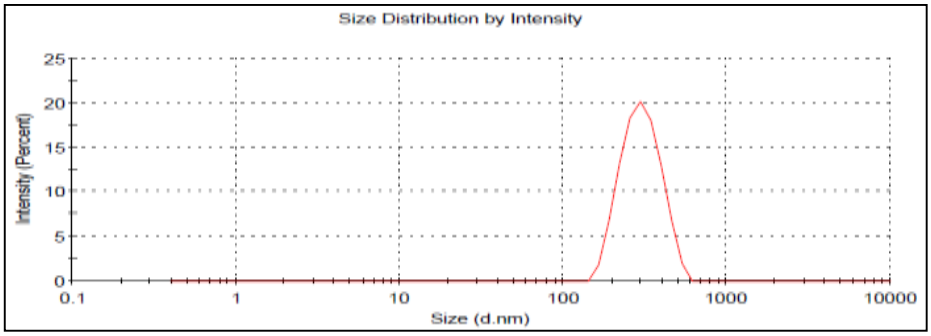
Table: 8 Evaluation results for Globule Size Analysis, Poly-dispersity Index and Zeta Potential

Formulation code	Globule Size (nm)	Poly-dispersity Index	Zeta Potential (mV)
OSF 1	278.7	0.07	-12.2
OSF 2	280.7	0.285	-9.91
OSF 4	208.7	0.254	-7.53
OSF 5	183.9	0.219	-9.30
OSF 6	184.1	0.408	-8.48

The droplet size of OSF-5 (183.9nm) and OSF-6 (184.1nm) was found to be smallest.

9.1: PARTICLE SIZE AND ZETA POTENTIAL OF OSF- 1

a) OSF-1 Particle Size



b) OSF-1 Zeta potential

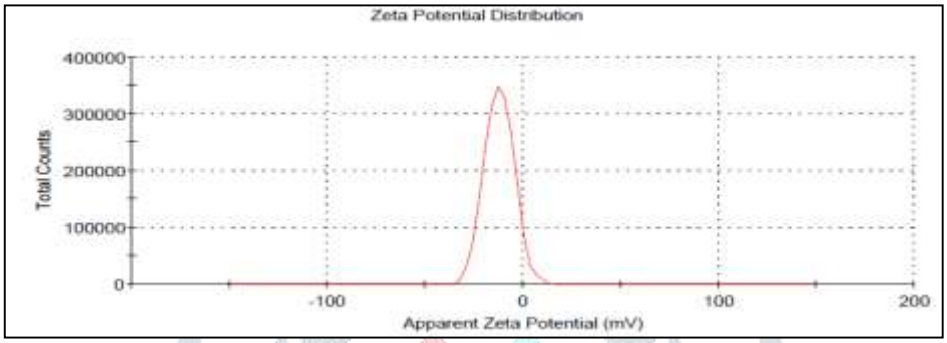
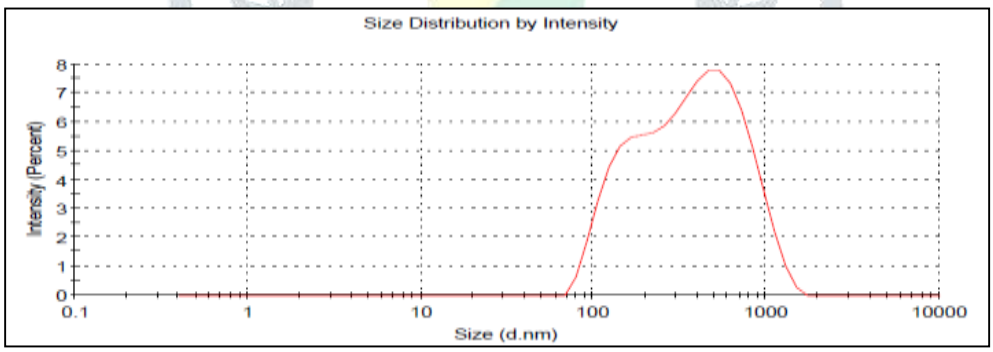


Fig. 10 OSF-1: Particle Size and Zeta potential result

9.2 PARTICLE SIZE AND ZETA POTENTIAL OF OSF- 2

a) OSF-2 Particle Size



b) OSF-2 Zeta potential

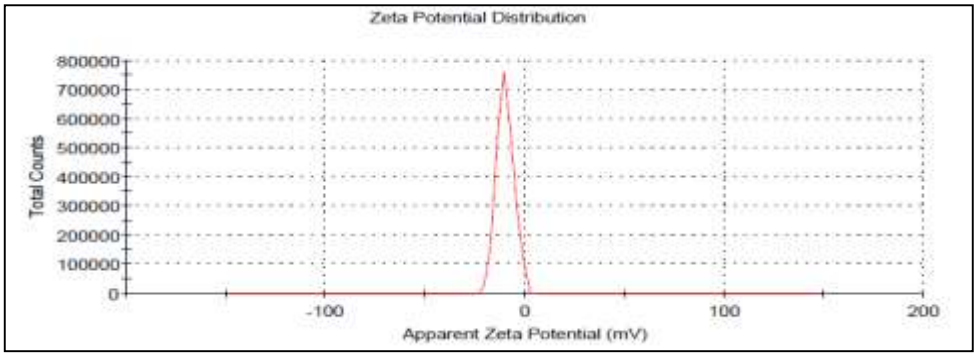
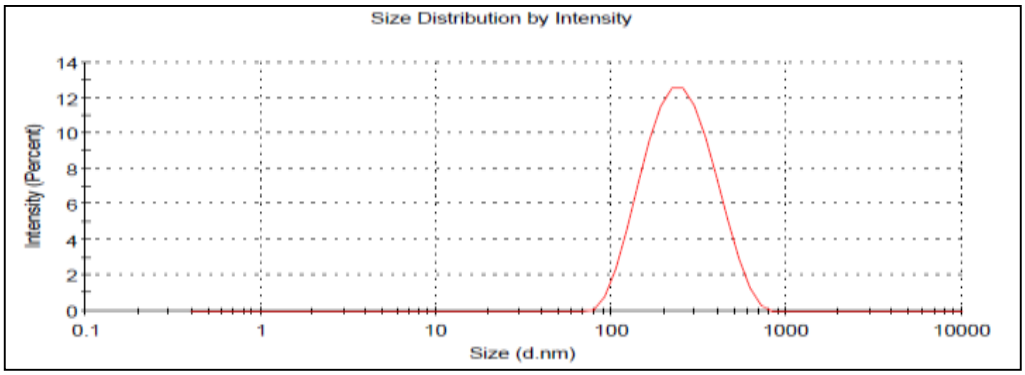


Fig. 11 OSF-2: Particle Size and Zeta potential result

9.3: PARTICLE SIZE AND ZETA POTENTIAL OF OSF- 4

a) OSF-4 Particle Size



b) OSF-4 Zeta Potential

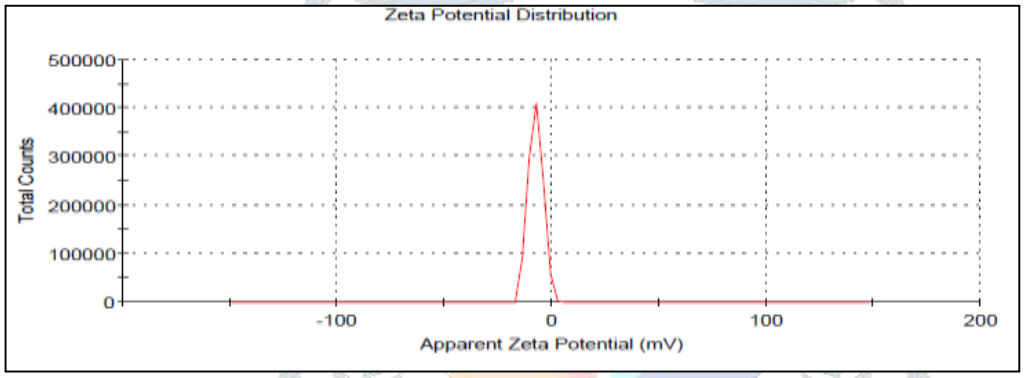
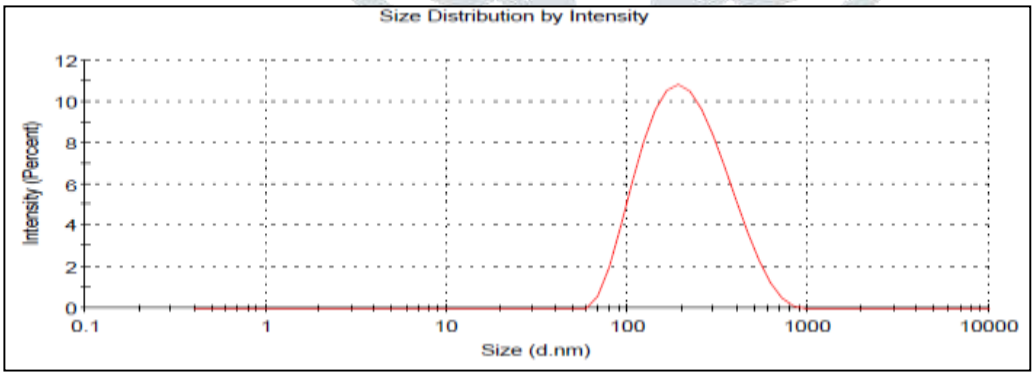


Fig. 12OSF-4: Particle Size and Zeta potential result

9.4: PARTICLE SIZE AND ZETA POTENTIAL OF OSF- 5

a) OSF-5 Particle Size



b) OSF-5 Zeta Potential

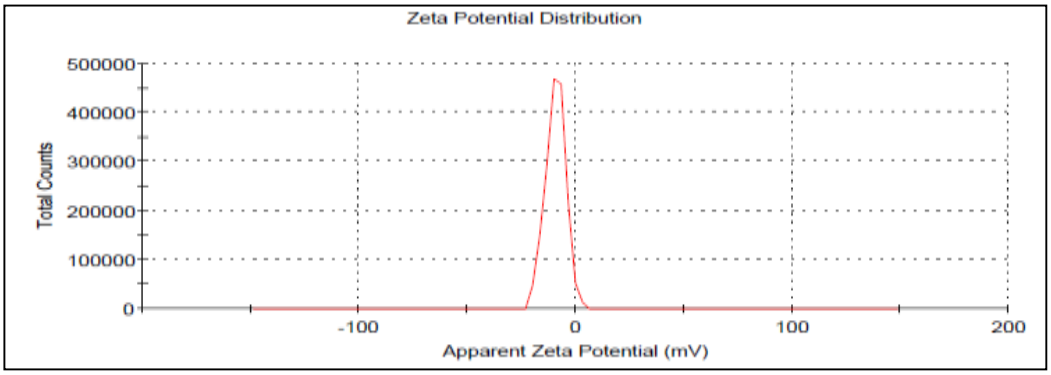
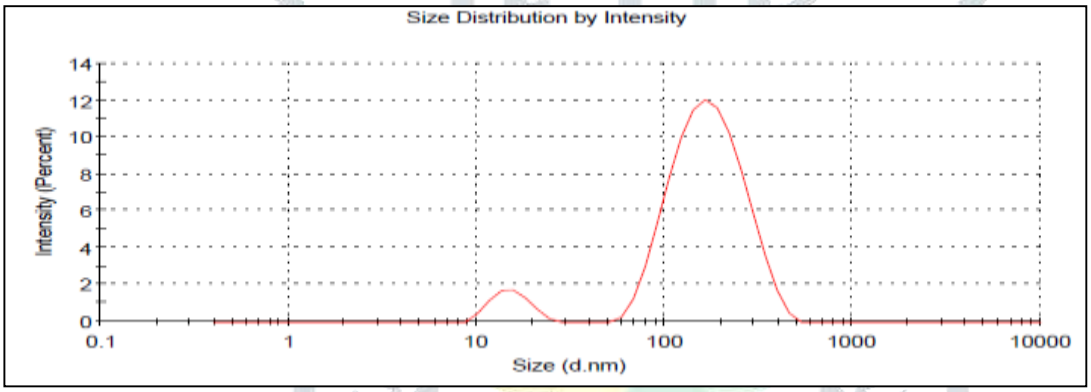


Fig. 13 OSF-5: Particle Size and Zeta potential result

9.5: PARTICLE SIZE AND ZETA POTENTIAL OF OSF- 6

a) OSF-6 Particle Size



b) OSF-6 Zeta Potential

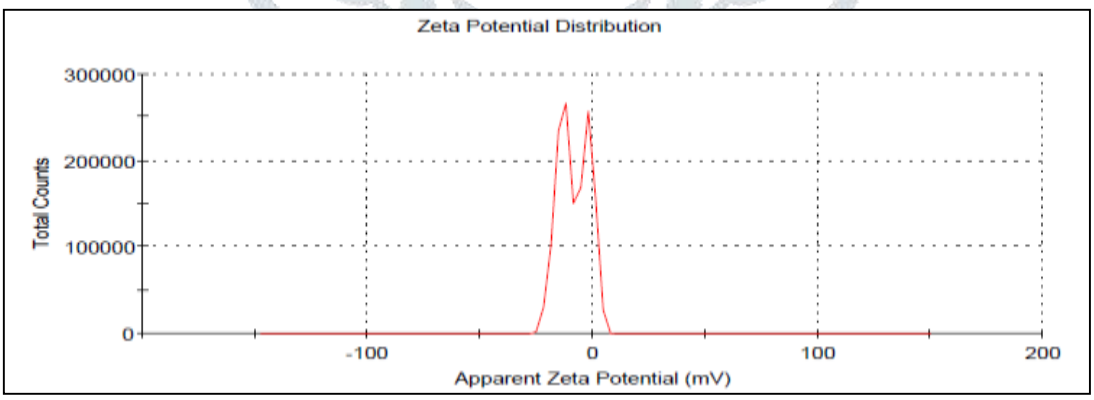


Fig. 14 OSF-6: Particle Size and Zeta potential result

D. **DISCUSSION**

(I)Formulation of Emulsion: From pseudo-ternary phase diagrams zone of emulsion was observed. Hence 9 different compositions were prepared by gently mixing drug incorporated oil, surfactants and Co-surfactants system.

Table: 9 Formulation codes of all the emulsion system prepared

Composition Ingredients (%w/w)	OSF1	OSF2	OSF3	OSF4	OSF5	OSF6	OSF7	OSF8	OSF9
Oil	90	80	70	60	50	40	30	20	10
S(mix)	10	20	30	40	50	60	70	80	90
Ratio	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2

G. CONCLUSION

Self-emulsifying formulations have shown tremendous potential in improving the bioavailability of therapeutic agents with limited aqueous solubility. Thus, liquid SEDDS of Olmesartan Medoxomil were successfully developed using Capmul MCM-E8, Tween-80 and PEG 200 as excipients by phase titration method. The optimized liquid SEDDS OSF-5 shows desirable percent transmittance, pH, Refractive index, viscosity, Emulsification time and % drug content. Converting the liquid SEDDS to solid dosage increases stability and ease of handling of micronized formulation. The optimized solid SEDDS formulation OSF-5 containing Olmesartan Medoxomil shows excellent flow properties, drug content, good particle size, Poly-dispersity index (PDI) and drug release. Thus, it can be concluded that the problem of efficiently delivering Olmesartan Medoxomil which is a poorly water soluble drug could be solved by lipid based drug delivery system that increase its solubility, enhances its bioavailability and hence reduces its dose. Hence, Olmesartan Medoximil can be formulated as solid self-emulsifying system which confirmed its potential as an innovative stable solid dosage form for oral delivery.

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