https://doi.org/10.48047/AFJBS.6.Si4.2024.1811-1826

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Preparation and Characterization of Self -Emulsifying Drug Delivery System of Olmesartan Medoxomil for Improving Solubility of BCS Class II Drug

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Article History
Volume 6, Issue Si4, 2024
Received: 01 June 2024
Accepted : 29 June 2024
Doi:
10.48047/AFJBS.6.Si4.2024.1811-1826

ABSTRACT

Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost-effective and leads the worldwide drug delivery market. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. It is estimated that 40% of active substances are poorly water soluble (water insoluble in nature). For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Various technological strategies are reported in the literature including solid dispersions, cyclodextrines complex formation, or micronisation, and different technologies of drug delivery systems. Including these approaches self-emulsifying drug delivery system (SEDDS) has gained more attention for enhancement of oral bio-availability with reduction in dose. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or micro-emulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

Keywords: Olmesartan medoxomil, Self-emulsifying drug delivery system, Bio-availability, Surfactants, Co-surfactants

Introduction

Approximately 40% of new drug have poor water solubility and the oral administration of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability and a lack of dose proportionality. To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions *(Chouhan et al., 2019).* SEEDS or self-emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or one or more hydrophilic solvents and co-solvents/ surfactants. Upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsions. Fine oil droplets would pass quickly from the stomach and promote widespread distribution of the drug throughout the GI tract, reducing the irritation commonly encountered during prolonged contact between bulk drug substances and the gut wall. Another advantage of SEEDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drugs with dissolution-limited oral absorption, these systems may offer an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles *(Patil et al., 2017).*

Mechanism of self-emulsifying drug delivery

- According to theory of thermodynamics, self-emulsification occurs when the entropy changes that facilitates dispersion is greater than the energy required to increase the surface area between the oil and aqueous phases of the dispersion.
- The formation of emulsion droplets is due to the formation of a complex film at the oil-water interface by surfactant and co-surfactants. Process of emulsification involves a change in free energy (G), which can be expressed as

  $G = \Sigma \dot{N} \pi r^2 \sigma$

  G - Free energy associated with the process (ignoring the free energy of the mixing),N - Number of droplets, r- Radius of droplet, σ- Interfacial energy with time.
- Two phases of emulsion tend to be separate, to reduce interfacial area and subsequently, the free energy of the system. Therefore, the emulsion is stabilized by emulsifying agents and forms a monolayer of emulsion droplets, ultimately reduces interfacial energy which acts as a barrier around oil droplets to prevent coalescence *(Pathak et al., 2010).*

Composition of SEDDS

- Drug (API)
- Excipients used in SEDDS
  - Surfactants
  - Oils
  - Co-surfactants

- **Drug**

The drug with poor aqueous solubility and high permeability are classified as BCS class IIdrug. These drugs are used for formulate SEDDS.

- **Surfactants**

Surfactant is the most essential component of SEDDS formulations. Natural origin surfactants are used because they are safer than the synthetic surfactants. Most widely used surfactants are the non- ionic surfactants (non -toxic as compared to ionic) with relatively high HLB value. Surfactant is made up of two parts that have different solvent affinities. The water phase prefers polar solvents, whereas the oil phase prefers non-polar solvents *(Pouton et al., 1985).*

- Surfactants strength ranging between 30-50% w/w is used to form stable SEDDS. Large quantity of surfactants irritates the GIT.
- Surfactants are amphiphilic in nature and they can dissolve relatively high amount of hydrophobic drugs compound.
- Regulate the droplet size and release rate.

Example: Tween 80, Tween 20, Span 80

- **Co-surfactants**

Co-surfactants in SEDDS formulation facilitate the dispersion process and increase the dissolution rate. Co-surfactants are most commonly used to dissolve large amounts of either hydrophilic surfactants or drugs in the lipid base *(Pouton et al., 1985).*

- Co - surfactants provide flexibility to interface.
- Co - surfactants are used to reduce the number of surfactants.

Examples: Propylene glycol,Transcutol HP, Polyethylene glycol

- **Oils**

Oil is considered as the most important excipient in the SEDDS. It is having an ability to solubilize the required dose of the hydrophilic drug as well as improves the self-emulsification and increases their transport via the intestinal lymphatic system, thereby improving absorption.In terms of SEDDS composition, medium- and long-chain triglycerides with varying saturation levels have been used. Because of their physicochemical properties, modified or hydrolyzed vegetable oils have shown a significant impact on the success of SEDDS *(Padole et al., 2012).*

- Increased absorption from the GIT.
- Help in solubilizing the lipophilic drug in a high amount.
- Oils protect the drug from degradation.

Examples: Corn oil, Peanut oil, Olive oil, Sunflower oil

Advantages of SEDDS

- Increased oral bioavailability.
- Better control of drug delivery profiles.
- Drugs are selectively targeted toward a specific absorption window in the GI tract.
- Drug(s) are protected from the hostile environment in the gut.
- Drug payloads are high.
- Reduced variability including food effects.
- Protect sensitive drug substances.
- Dosage forms (liquid or solid).
- Deliver peptides that are prone to enzymatic hydrolysis**.**
- When polymer is incorporated in SEDDS, it gives a prolonged release of medicaments *(Patel et al., 2008).*

Disadvantages of SEDDS

- Drugs with chemical instabilities and high surfactant content may irritate the GI tract.
- Co solvents can migrate into the shells of soft or hard gelatin capsules, causing precipitation drugs to form *(Sharma et al., 2012).*
- Because of the dilution effect of the hydrophilic solvent, the drug's precipitation tendency may be increased after dilution.
- Validation of multi-component formulations becomes more difficult.

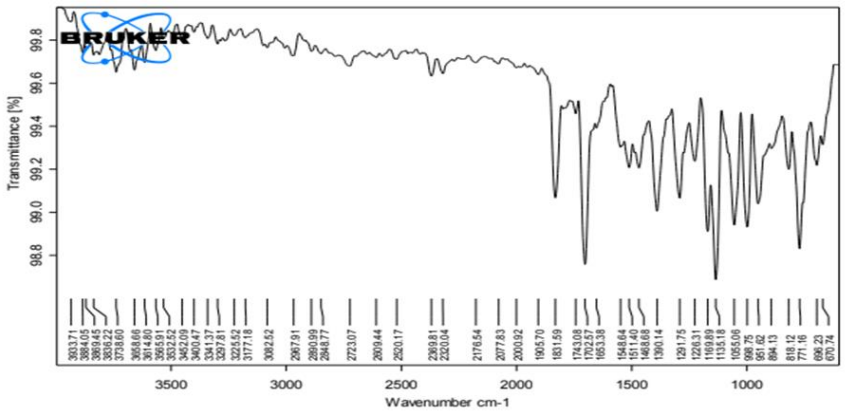
Factors affecting SEDDS formulation:

The following factors are discussed further below:

1. **Drug nature and dosage:** Drug must be soluble in one or more formulation components in order to be manufactured from high-dose formulations. Drug delivery via SEDDS is most difficult when the drug is poorly soluble in lipids.
2. **The lipophilic phase's polarity**: The polarity of the lipid phases one of the factors that govern the drug release from the micro emulsion. Droplet polarity varies with HLB value, unsaturation degree, and FA chain length and the molecular weight of micro ionized drug *(Trivedi et al., 2020).*

Characterization

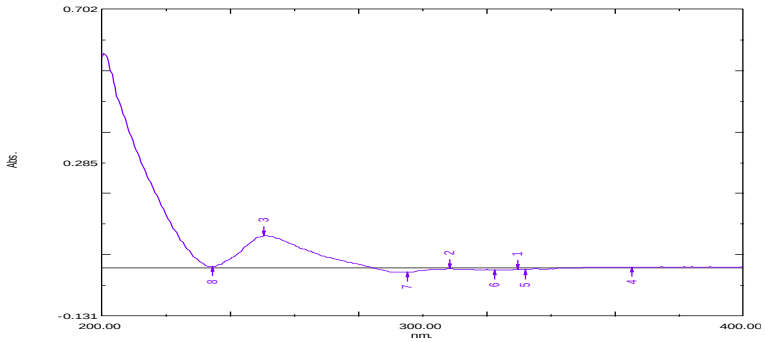
FTIR Spectroscopy of pure drug: The spectrum was recorded for pure drug over the range of 400-4000 cm^{-1} with a FTIR spectrophotometer. The sample was pressed and scanned. In the spectra that were appeared on the screen the baseline was corrected. The drug was identified by infrared spectroscopy and characteristic peak obtained compared with standard spectra of pure drug reported in official monograph. The IR spectra of pure drug is shown in (Figure)and it showed the characteristic peaks at 1153.18 due to C=0 stretching, at 3080.52 due to O-H stretching, 3400.47 due to N-H stretch, 1169.89 due to C-N stretching, 2967.91 due to C-H stretching, 1390.14 due to N=O stretching.



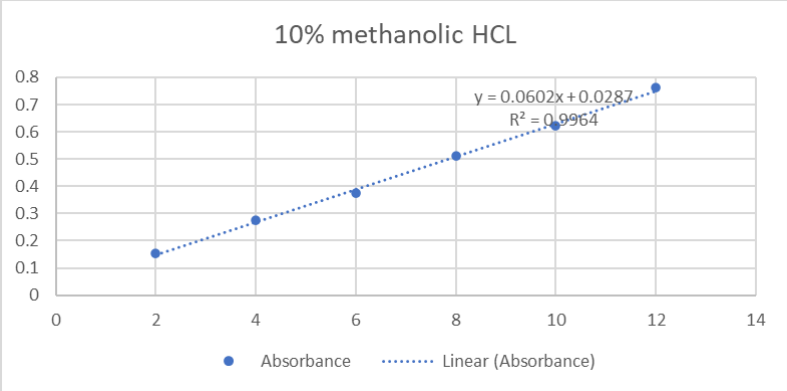
Functional group	Standard Frequency	Observed Frequency
N-H Stretching	3300-3500	3400.47
C-H Stretching	2850-3000	2967.91
O-H Stretching	3300-2500	3080.52
N=O Stretching	1350-1550	1390.14
C-N Stretching	1220-1020	1169.89
C=O Stretching	1000-1300	1135.18

STANDARD curve of OLM:

Determination of λmax of Olmesartan medoxomil: The stock solution was prepared by dissolving the 100 mg of drug (Olmesartan medoxomil) in 100 ml methanol. To remove any air bubble, the solution was sonicated for 15 minutes. The stock solution was diluted with 0.1 N HCL to obtain different concentrations and the diluted solution was scanned in 200-400nm range to determine the absorbance spectrum of corresponding solutions.



Preparation of calibration curve of Olmesartan medoxomil: Using 0.1 N HCL, aliquots of varying concentrations (2, 4, 6, 8, 10, and 12) were prepared from the above prepared stock solution. Before scanning the solution with a UV spectrophotometer for the linearity range, the solution was filtered. Each concentration absorbance at 250 nm was measured. For Olmesartan medoxomil, the linearity of the solution was in the2-12 ug/ml concentration range.



Solubility study: 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. In the case of SEDDS initially preliminary solubility analysis was carried out to select the appropriate excipient from various oils (Castor oil, Sunflower oil, Olive oil, Peppermint oil and Lavender oil), surfactants (Tween 80, Tween 20, Span 80, and Span 20), co-surfactants (PEG 400, PEG 200, PEG). Based on drug solubility, Sunflower oil, Tween 80 and PEG 400 were selected as oil, surfactant and co-surfactant respectively.
Solubility of Olmesartan medoxomil in various oil, surfactant, and co-surfactant is shown in table 1-3.

Table1: Solubility of Olmesartan medoxomil in different oils

Sr. No.	Oils	Solubility(mg/ml)
1.	Castor oil	26.47
2.	Sunflower oil	44.54
3.	olive oil	40.25
4.	Peppermint oil	22.16
5.	Lavender oil	32.56

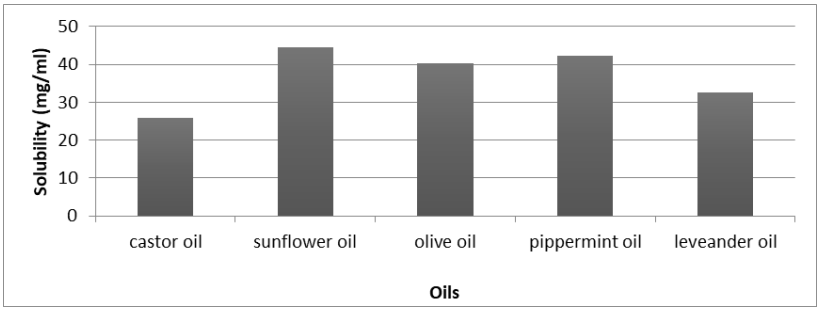


Table2: Solubility of Olmesartan medoxomil in different surfactants

Sr. No.	Surfactants	Solubility(mg/ml)
1.	Tween 80	36.23
2.	Tween 20	35.56
3.	Span 80	28.18
4.	Span 20	33.96

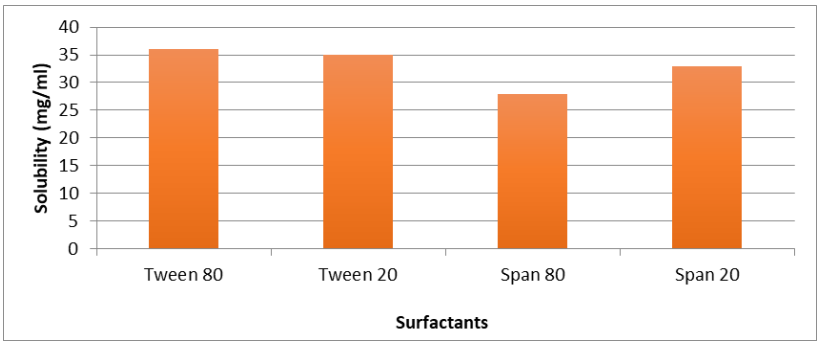
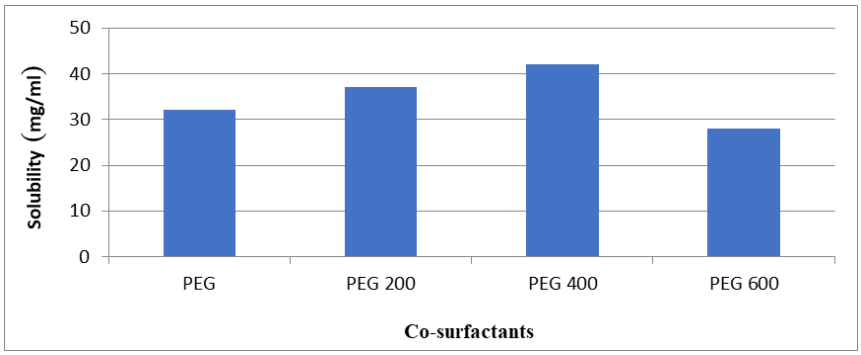


Table 3: Solubility of Olmesartan medoxomil in different co-surfactants

Sr. No.	Co-surfactants	Solubility(mg/ml)
1.	PEG	32.31
2.	PEG 200	37.71
3.	PEG 400	42.24
4.	PEG 600	28.45

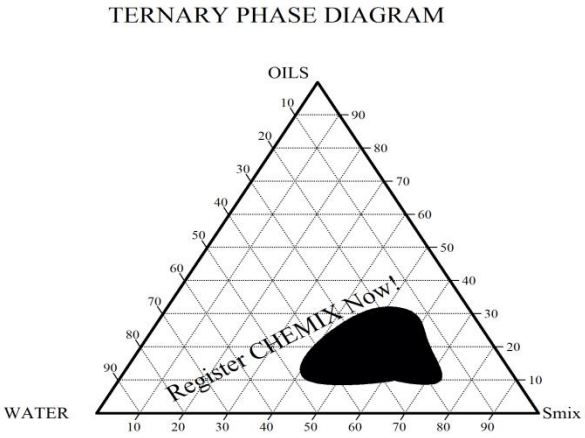


Pseudo ternary phase diagram: On the basis of the solubility study of drug, oil, surfactant and co-surfactant were selected. Distilled water was used as a water phase for phase diagram study. Surfactant and co-surfactant (Smix) were mixed in different weights ratios (1:1, 1:2, 2:1, 3:1 and 4:1). These Smix ratios were chosen in increasing concentration of surfactant with respect to co-surfactant, and increasing concentration of co-surfactant with respect to surfactant. For each phase diagram, oil and specific Smix ratio were mixed in different ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, and 1:9). Pseudo-tertiary phase diagrams were developed using dilution method. Dilution with distilled water was done with each weight ratio of oil

and Smix and visual observation was carried out for transparent and easily flowable O/W emulsion. The results obtained were marked on a pseudo-three-component phase diagram with one axis representing oil phase, other representing mixture of surfactant and co-surfactant at fixed weight ratios and third representing water phase.Ternary phase diagram was constructed using CHEMIX school software:

Sr.No.	% Sunflower oil	% Tween 80	% PEG 400	Appearance of emulsion	Drug precipitation
Smix Ratio (1:1)					
1	10	45	45	Transparent	No
2	20	40	40	Transparent	No
3	30	35	35	Turbid	No
4	40	30	30	Turbid	No
5	50	25	25	Turbid	No
6	60	20	20	Turbid	No
7	70	15	15	Turbid	No
8	80	10	10	Turbid	No
9	90	5	5	Turbid	No
SmixRatio(2:1)					
1	10	60	30	Transparent	No
2	20	53.3	26.7	Transparent	No
3	30	46.7	23.3	Transparent	No
4	40	40	20	Turbid	No
5	50	33.3	16.7	Turbid	No
6	60	26.7	13.3	Turbid	No
7	70	2	10	Turbid	No
8	80	13.3	6.7	Turbid	No
9	90	6.7	3.3	Turbid	No
SmixRatio(3:1)					
1	10	67.5	22.5	Transparent	No
2	20	60	20	Transparent	No
3	30	52.5	17.5	Transparent	No
4	40	45	15	Transparent	No
5	50	37.5	12.5	Turbid	No
6	60	30	10	Turbid	No
7	70	22.5	7.5	Turbid	No
8	80	15	5	Turbid	No
9	90	7.5	2.5	Turbid	No
SmixRatio(4:1)					
1	10	72	18	Transparent	No
2	20	64	16	Transparent	No
3	30	56	14	Transparent	No
4	40	48	12	Turbid	No

5	50	40	10	Turbid	No
6	60	32	8	Turbid	No
7	70	24	6	Turbid	No
8	80	16	4	Turbid	No
9	90	8	2	Turbid	No



Pseudo ternary phase diagram

Preparation of SEDDS: A series of SEDDS formulations were prepared with varying ratios of oil (20-40 %), surfactant (30-70%) and co-surfactant (10-50 %). A single dose of Olmesartan Medoxomil (20 mg) was incorporated in all formulations. 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 to obtain a homogenous isotropic mixture. The SEDDS formulations were stored at ambient temperatures until further use.

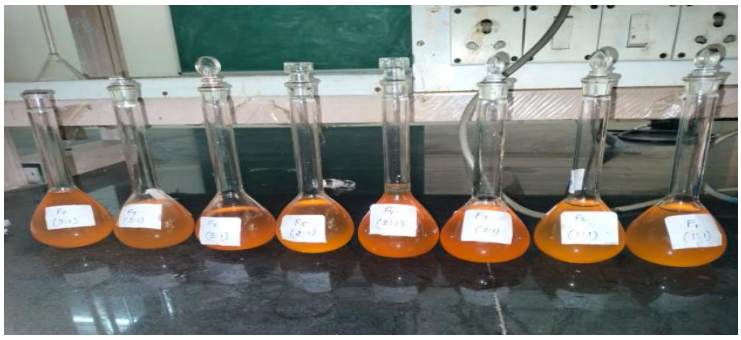


Table 4: Composition of prepared SEDDS of Olmesartan medoxomil

Formulation	Surfactant: Co-surfactants	Oil:Smix	Sunflower oil	Tween 80	PEG 400
F1	1:1	1:9	10	45	45
F2		2:8	20	40	40
F3	2:1	1:9	10	60	30
F4		2:8	20	55.3	26.7
F5		3:7	30	46.7	23.3
F6	3:1	1:9	10	67.5	22.5
F7		2:8	20	60	20

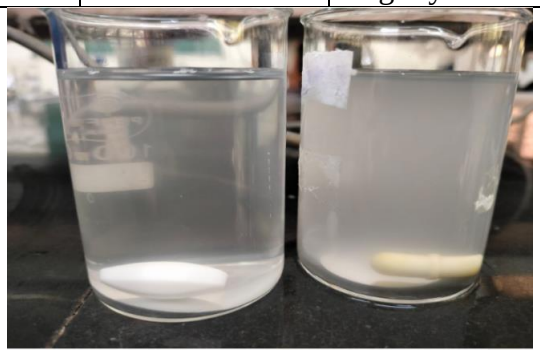
F8		3:7	30	52.5	17.5

Characterization of OLM loaded SEDDS

Visual observation: With the use of visual observation method, the tendency of formation of emulsion was observed. Visual observation test was performed for different ratios by keeping the surfactant and co-surfactant ratio (Smix) as1:1, 2:1 and 3:1. Therefore, these ratios were selected for the formulation of SEDDS.Ratio 1:9(F1), 1:9(F3), 2:8(F4), 1:9(F6) and 2:8(F7) showed rapid formation of micro emulsion with transparent appearance. Ratio 2:8(F2), 3:7(F3), 3:7(F8) showed slightly clear appearance.

Table 5: Visual observation analysis of SEDDS formulations

S.No.	Formulation code	Visual observation
1	F1	Transparent
2	F2	Slightly clear
3	F3	Transparent
4	F4	Transparent
5	F5	Slightly clear
6	F6	Transparent
7	F7	Transparent
8	F8	Slightly clear



Dispersibility test:

- The test for dispersibility was visually assessed and a fine milky emulsion was formed within 40 second for F4, F8 formulation, which revealed that these formulations belonged to Grade C.
- F3, F6 and F7 formed clear emulsion within 30 seconds and these formulations belonged to Grade A.
- F1, F2 formed less clear emulsion within 30 seconds and these formulations belonged to Grade B.
- F5 formed white emulsion within 1 min and these formulations belonged to Grade D.

Table 6: Dispersibility test and self-emulsification time of SEDDS formulations

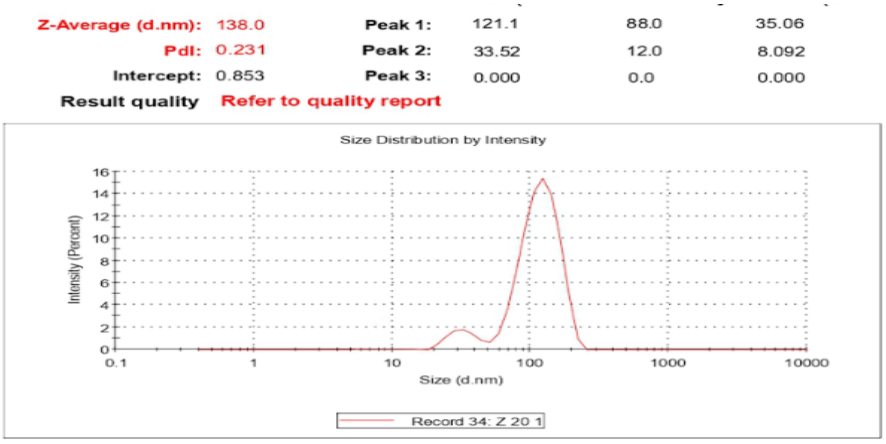
Formulation	Dispersibility	Self-emulsification time
F1	Grade B(less clear emulsion)	30 sec
F2	Grade B(less clear emulsion)	30 sec
F3	Grade A(clear emulsion)	30 sec
F4	Grade C(fine milky emulsion)	40 sec
F5	Grade D(white emulsion)	1 min
F6	Grade A(clear emulsion)	30 sec
F7	Grade A(clear emulsion)	30 sec

F8	Grade C(fine milky emulsion)	40 sec

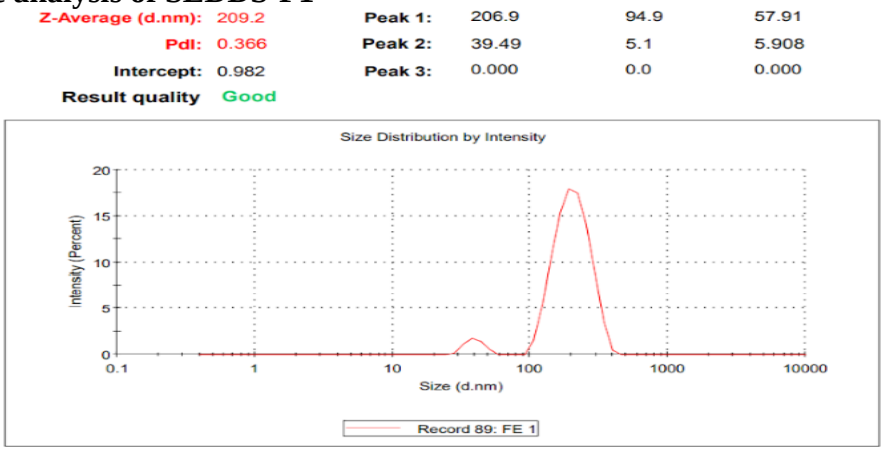
Droplet size analysis: The particle size of OLM-SEDDS was identified by using a Zeta sizer (Nano-ZS, Malvern instruments, UK) at 25°C. An increase in the ratio of oil phase resulted in a proportional increase in globule size, because of the simultaneous decrease in the Smix proportion. Therefore, the particle size of F2, F5, F7, F8 is high as the amount of oil phase is high (20-30%) in these formulations. A lower or moderate concentration of sunflower oil along with moderate or high concentration of Tween 80 resulted in smaller particle size (F1, F3, F4, and F6).

Table 7: Droplet size analysis of SEDDS formulations

Formulation	Oil:Smix	Droplet size
F1	1:9	138.0
F2	2:8	209.2
F3	1:9	125.3
F4	2:8	175.0
F5	3:7	243.6
F6	1:9	141.4
F7	2:8	227.4
F8	3:7	279.4

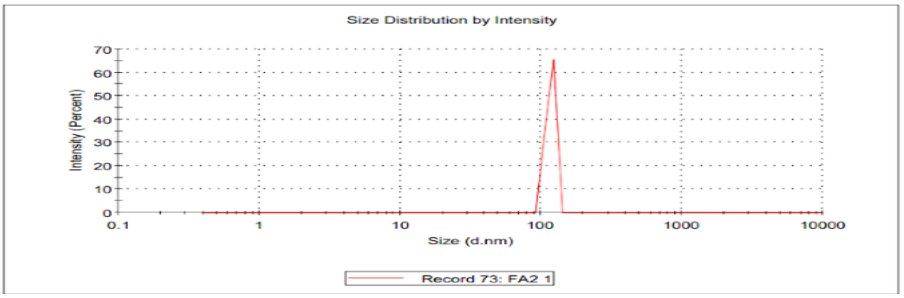


Droplet size analysis of SEDDS-F1



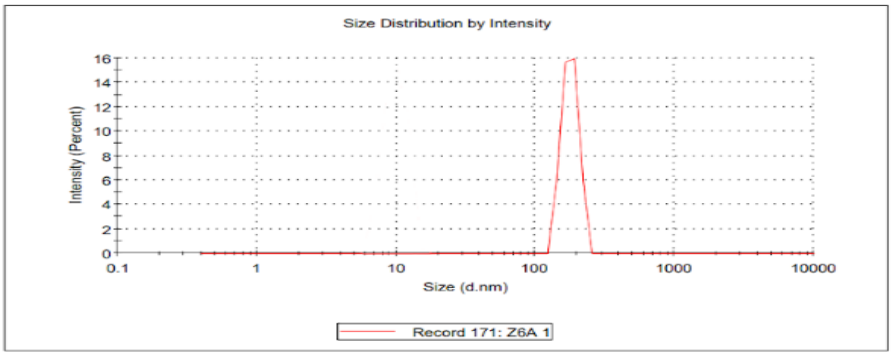
Droplet size analysis of SEDDS-F2

Z-Average (d.nm):	125.3	Peak 1:	116.7	100.0	7.945
PdI:	0.346	Peak 2:	0.000	0.0	0.000
Intercept:	1.20	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



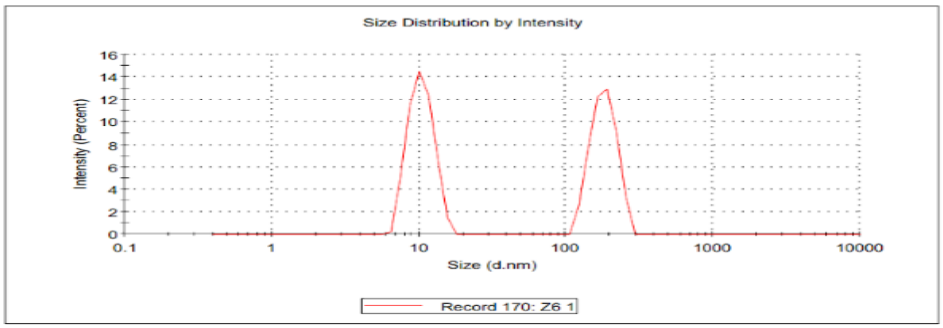
Droplet size analysis of SEDDS-F3

Z-Average (d.nm):	175.0	Peak 1:	178.3	100.0	23.33
PdI:	0.498	Peak 2:	0.000	0.0	0.000
Intercept:	0.938	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



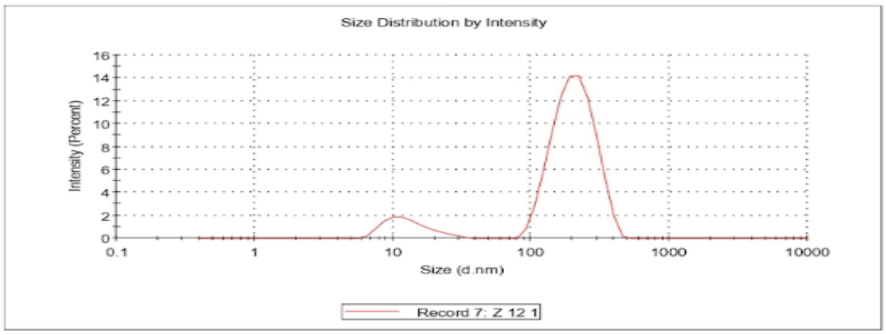
Droplet size analysis of SEDDS-F4

Z-Average (d.nm):	243.6	Peak 1:	10.51	51.9	2.004
PdI:	0.299	Peak 2:	182.3	48.1	34.73
Intercept:	0.861	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



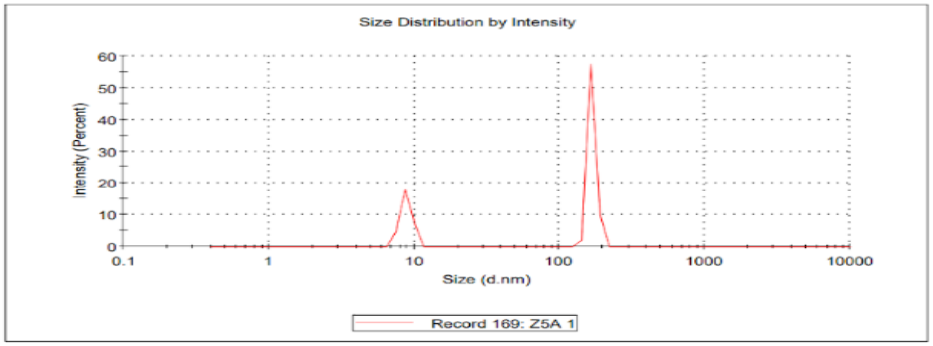
Droplet size analysis of SEDDS-F5

Z-Average (d.nm):	141.4	Peak 1:	212.0	88.4	69.43
PdI:	0.351	Peak 2:	13.51	11.6	5.427
Intercept:	0.943	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



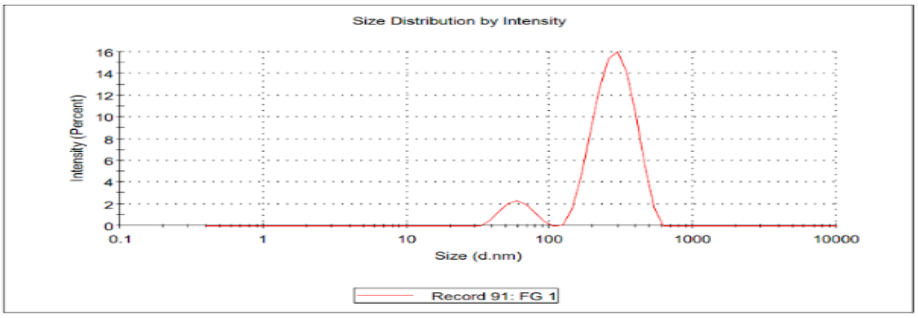
Droplet size analysis of SEDDS-F6

Z-Average (d.nm):	227.4	Peak 1:	167.3	69.5	10.14
PdI:	0.429	Peak 2:	8.876	30.5	0.8186
Intercept:	0.994	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



Droplet size analysis of SEDDS-F7

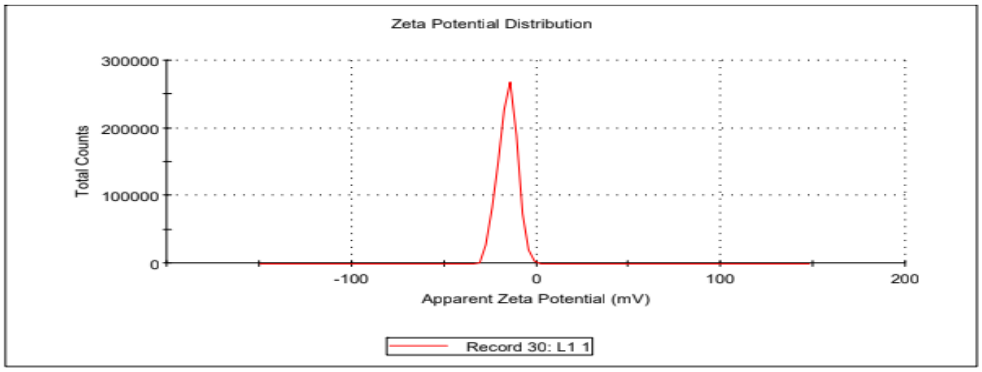
Z-Average (d.nm):	279.4	Peak 1:	291.7	90.2	86.97
PdI:	0.404	Peak 2:	59.59	9.8	13.30
Intercept:	0.950	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				



Droplet size analysis of SEDDS-F8

Zeta potential determination: SEDDS F3 reports negative zeta potential value.The surfactant (Tween 80) and co-surfactant (PEG 400) used in this study are nonionic which do not contribute any charge to the emulsion particle. This indicates that negative charge particle do not affect the stability of emulsion. Stability of colloidal system is dependent on magnitude of zeta potential. If particles have high negative or high positive zeta potential, it will give more stability to dispersion due to repelling of globules and if particles have less zeta potential, then less force is available to repel globules so particles come together and leads to instability of dispersion. +30 or -30mV zeta potential value is dividing line for deciding stable or unstable dispersion. Formulation F3 indicates the high magnitude of negative zeta potential which is near to range.

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-15.6	Peak 1: -15.6	100.0	5.17
Zeta Deviation (mV):	5.17	Peak 2: 0.00	0.0	0.00
Conductivity (mS/cm):	0.115	Peak 3: 0.00	0.0	0.00
Result quality	Good			



Zeta potential analysis of SEDDS-F3

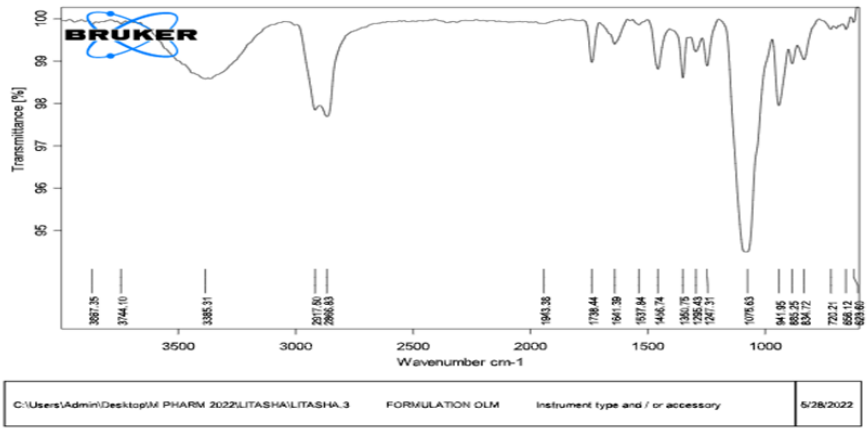
FT-IR spectroscopy:

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-1and 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 excipients, it was observed that all the characteristic peaks of Olmesartan medoxomil were present in the combination spectrum, thus indicating compatibility of the drug and excipients.

Table 8: FT-IR spectroscopy of pure drug and SEDDS-F3

Functional group	Peak of pure drug	Peak of SEDDS-F3	Comments
N-H Stretching	3400.47	3385.31	No effect
C-H Stretching	2967.91	2866.83	No effect
O-H Stretching	3080.52	2917.50	No effect
N=O Stretching	1390.14	1350.75	No effect
C-N Stretching	1169.89	1295.43	No effect
C=O Stretching	1135.18	1075.63	No effect



Phase separation study:

Centrifugation study

Formulations were centrifuged at 3000rpm for 30 min and examined for phase separation.After subjecting the formulation to centrifugation, it has been observed visually

that formulations pass this test and showed good stability with no phase separation, creaming and cracking.

Conclusion

SEDDS formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. Self-emulsifying drug delivery system can be used for the formulations of drugs compounds with poor aqueous stability. Development of this technology SEDDS will continue to enable novel applications in drug delivery system. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents.

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