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# FORMULATION AND EVALUATION OF SMEDDS CONTAINING EZETIMIBE BY EMPLOYING ARACHIS OIL AS OIL AND TWEEN 80, PEG 400 AS SURFACTANT SYSTEM

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## ABSTRACT
Solubility is the important process for most of the drug to solubilize in a given solvent to give homogenous solution. The greater the solubility of drug, the greater will be the systemic dissolution showing desired pharmacological response. New techniques have been developed to improve the solubility rate of poorly soluble drugs. Solid dispersion, Complexation, Particle size reduction, co-solvency, etc. Among which, a recent approach lipid base formulations (SMEDDS) are attracting the formulation scientists. These lipid based formulations include SMEDDS, SNEDDS. SMEDDS are nothing but the emulsion containing oil, surfactant, co-surfactant and drug which form oil in water emulsion upon mild agitation with aqueous phase. In the present study SMEDDS containing Ezetimibe, a BCS class II drug is formulated. As Ezetimibe is insoluble in water, lipid based formulations SMEDDS are developed by employing arachis oil as lipid phase, Tween 80, PEG400 were selected as surfactant mixture. The better formulations were selected based on the evaluation parameters like drug content, %transmittance, drug release studies.

**KEYWORDS:** SMEDDS (self micro emulsifying drug delivery system), Ezetimibe, PEG 400, Tween 80, Ternary diagram.

## INTRODUCTION
Oral drug delivery is the most common route used to deliver drugs. Drugs which are highly soluble/hydrophilic can be easily delivered by oral route which increase the bioavailability of drug in body. Drugs which are lipophilic offer least advantage because of their low aqueous[1-4] solubility. Various solubility enhancement techniques like solid dispersion, complexation, salt formation of drug, co-solvency, use of surfactants etc., are employed to improve the solubility and bioavailability of poorly aqueous soluble drugs. Each of this technique provides some disadvantages.

Oral delivery of poorly water soluble drugs using lipid as vehicle is a new and recent approach. Lipid based formulations are such as liposome, solid lipid nanoparticle, self-emulsifying administration of lipids along with lipophilc drugs offer better advantages by increasing the bioavailability of drugs and prolongs the GI residence time of drug.

Among the various lipid based formulation self-emulsifying formulations are receiving greater attention by formulation scientist as they are effect in hydrophobic drug delivery, increased stability, self-dispersing nature, ease of scale up.[5-8] These systems are developed by using a lipid carrier which improves the gastro intestinal absorption of poorly water soluble drugs, allows the drug to remain in dissolved state by protecting the drug from enzymatic reaction, thermodynamically stable, easily manufactured and suitable for oral drug delivery. Compounds used in this system include oil, surfactant, and co-surfactant.

The function of oil in this system is to solubilize the lipophilic drug in order to improve the drug loading and bioavailability. Medium chain triglycerides are most commonly used[9-14] as they are resistant to precipitation. Hydrophobic drugs are easily solubilized in oil. As solubility is limited in oils, micro emulsification of oil and surfactant is employed which enhances the drug solubility in oils. Enhancement of drug solubility primarily depends on factors such as efficiency and rapidity to micro emulsify the selected oil, solubility of drug in surfactant. Nonionic surfactants are commonly preferred in formulation as they have less[15-21] CMC value, they are less toxic, provides a greater emulsion stability over a wide range of pH and ionic strength. Concentration of co-surfactant plays a major role in lipid based formulation. Selection of surfactant and co-

surfactant is necessary for the solubilization of drug. Organic solvents such as ethanol, propylene glycol, polyethylene glycol are suitable for oral drug delivery.

## MATERIALS AND METHOD

### Materials

Ezetimibe is obtained as gift sample from Sun pharma, Arachis oil, Tween 80, PEG 400, MCC pH 102, and all other ingredients used are of pharmacoepial standards.

### Solubility study

The solubility of Ezetimibe is checked in various compounds like oil, surfactants, and co-surfactants respectively. Excess amount of drug was added in each test tube containing 5ml of solvent, the test tubes were placed in orbital shaker for 48hrs to achieve solubility equilibrium. The supernatant was separated and filtered through a membrane filter to remove the undissolved drug. Solubility of Ezetimibe was determined by analyzing the filtrate at 315nm.

### Construction of ternary phase diagram

Phase behavior of each SMEDDS is studied carefully by using the phase diagram. It is one of the important characteristics of SMEDDS to show the changes when the system is diluted, which may cause drug precipitation. Therefore, phase behavior of each SMEEDS should be carefully studied. Based on solubility shown by drug in different ratios of surfactants the ternary diagrams were developed.

### Formulation of SMEEDS of Ezetimibe

Based on ternary diagrams, a series of formulations were prepared by using different ratios of oil: $S_{mix}$. The formulations were stored at room temperature until further use.

**Table 1: Different formulations prepared with different ratios of oil: $S_{mix}$**

| Formulation No | Smix (Tween80 : PEG 400) | Oil : Smix |
|---|---|---|
| A1 | 1:1 | 1:1 |
| A2 | | 1:2 |
| A3 | | 1:3 |
| A4 | | 2:1 |
| A5 | | 3:1 |
| A6 | 1:2 | 1:1 |
| A7 | | 1:2 |
| A8 | | 1:3 |
| A9 | | 2:1 |
| A10 | | 3:1 |
| A11 | 1:3 | 1:1 |
| A12 | | 1:2 |
| A13 | | 1:3 |
| A14 | | 2:1 |
| A15 | | 3:1 |
| A16 | 2:1 | 1:1 |
| A17 | | 1:2 |
| A18 | | 1:3 |
| A19 | | 2:1 |
| A20 | | 3:1 |

## CHARACTERIZATION

### Characterization of SMEDDS

SMEDDS pre-concentrate equivalent to dose of drug was diluted with diluted with distilled water. This micro emulsion was taken for in vitro characterization.

### Appearance

Appearance of all the formulation SMEDDS (A1-A20) was tested visually against white and black background.

### Conductance

The electro conductance of resultant micro emulsion system was measured by using conductivity meter (CM 180, ELICO). Each measurement was carried out in triplicate.

### %Transmittance

The percentage transmittances of samples (A1-A20) are measured by using colorimeter (CL 223 colorimeter, ELICO)

### Emulsification of samples

To assess emulsification properties of prepared formulations (A1-A20) each formulation was introduced into a 250ml glass beaker containing distilled water at room temperature and contents were agitated gently. The tendency to form clear or transparency emulsion is considered as good, when the formation was poor or milky in appearance then it is considered as bad emulsion.

**Stability studies**

The stability of lipid based formulation is essential for its performance, which can be adversely effected by the precipitation of drug. In addition formulations having poor stability leads to phase separation affecting the formulation performance and visual appearance. Stability studies of formulations are performed by heat cooling, centrifugation, and freeze thaw cycle.

**1. Heat cooling cycle**

Six cycles were carried out between 40˚c to 45˚c. In between these temperatures, formulations were stored not less than 48hrs. The formulations which are stable at these temperatures are subjected to centrifugation.

**2. Centrifugation**

The formulations which passed through above test are centrifuged at 3500rpm for 30min. The formulations that did not show phase separation were taken for freeze thaw test.

**3. Freeze thaw cycle**

Freeze thaw cycles were carried out between -20˚c to +25˚c. Formulations are stored at each temperature not less than 48hrs.

**Droplet size analysis**

The droplet size of emulsions were determined by using zetasizer which is able to measure sizes between 10 and 500 nm. Light scattering is monitored at 25˚c at a 90˚ angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the systems compatibility with excess water.

**Zeta potential**

The charge of the oil droplets in conventional SMEDDS is negative due to presence of free fatty acids. The zeta potential values were determined by using Zetasizer.

**Preparation of solid SMEDDS**

The prepared SMEDDS are converted into solid dosage forms by adding excipients like MCC pH 102 the resultant mixture is weighed and filled in hard gelatin capsule. These are stored for further analysis.

**Drug content**

The formulated SMEDDS equivalent to 10mg of drug is taken and dissolved in methanol and the resultant sample with proper dilutions are checked for their absorbance in UV (UV-2203, Systronics) at 232 nm and percent drug content is calculated.

**Uniformity weight of capsule**

Fill the capsule shell with formulation (A1-A20). Weight of individual capsule should be noted and average weight was calculated. Not more than two individual weight deviate from average weight.

**In vitro dissolution rate study**

In vitro dissolution rate study of all the prepared formulations (A1-A20) containing 40mg of dug Ezetimibe was performed by using USP dissolution apparatus I (basket) (USP TDL-14L dissolution tester, electro lab). Acetate buffer of pH 4.5 was used as dissolution media maintained at 37˚c and 75rpm. 5ml of aliquots were withdrawn at specific time intervals and the same amount of fresh buffer was replaced to maintain sink conditions. The collected aliquots were analyzed for drug content at 232nm using UV-Visible spectrophotometer (UV-2203, Systronics). The test was performed in triplicate. The prepared formulations (A1-A20) were compared with the marketed product (Ezedoc® 10) of Ezetimibe, with respect to drug release.

## RESULTS AND DISCUSSION

**Solubility study**

The solubility studies of Ezetimibe in different compounds

**Table 2: Solubility of drug in different surfactant.**

| S.no | Solvent | Amount of drug dissolved (gm) |
|---|---|---|
| 1 | Ethanol | 2 |
| 2 | PEG 400 | 2.5 |
| 3 | Propylene glycol | 1 |
| 4 | Tween 80 | 3 |
| 5 | Coconut oil | 1.5 |
| 6 | Arachis oil | 1 |
| 7 | Soybean oil | 0.5 |

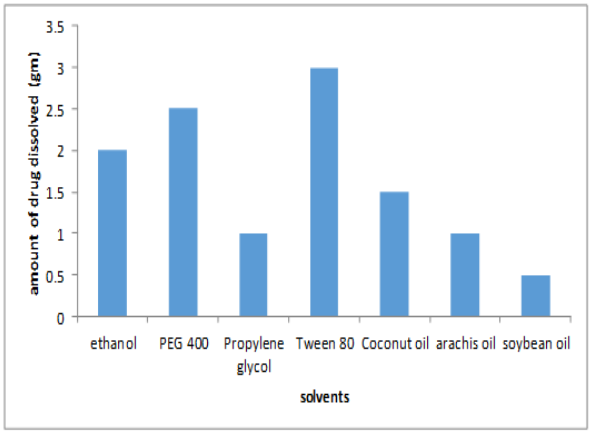


**Fig 1: Solubility profile of Ezetimibe in various solvents.**

**Solubility study of Ezetimibe in various compounds**

The solubility of drug was checked in various compounds and the values ranges from 23-48mg/ml. Based on solubility studies coconut oil was selected as oil phase. Tween 80 PEG 400 and labrasol selected as surfactant and co-surfactant further the ratios of surfactant: co-surfactant was fixed from solubility data obtained from the studies of different ratios of surfactant: co-surfactant.

**Table 3: Solubility of drug in different ratios of surfactant and co-surfactant (S mix).**

| S.No | S: Co S($S_{mix}$) | Amount of drug dissolved (mg) |
|---|---|---|
| 1 | 1:1 | 300 |
| 2 | 1:2 | 500 |
| 3 | 3:1 | 200 |
| 4 | 4:1 | 120 |
| 5 | 5:1 | 100 |
| 6 | 1:3 | 450 |
| 7 | 1:2 | 350 |

From the above study 1:1, 1:2, 1:3 and 2:1 were selected further for formulation of SMEDDS

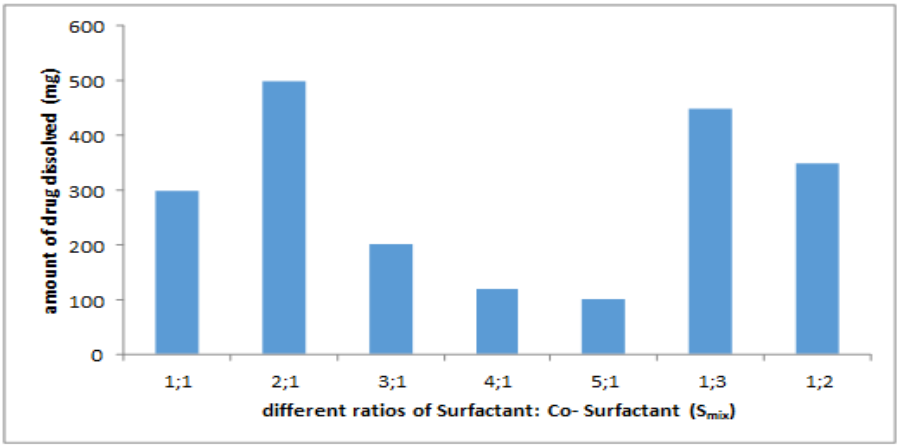


**Fig. 2: solubility profile of drug in different Smix ratio.**

The solubility studies of Ezetimibe in different ratios of Smix were carried out and it was clear from the studies that 1:1, 1:2, 1:3 and 2:1 ratio of Smix has shown better solubility of drug when compared to other ratios.

**Construction of ternary phase diagram**

Oil, water and $S_{mix}$ were taken as each apex of ternary graph and ternary diagrams were constructed separately for each group to identify the micro emulsion region.

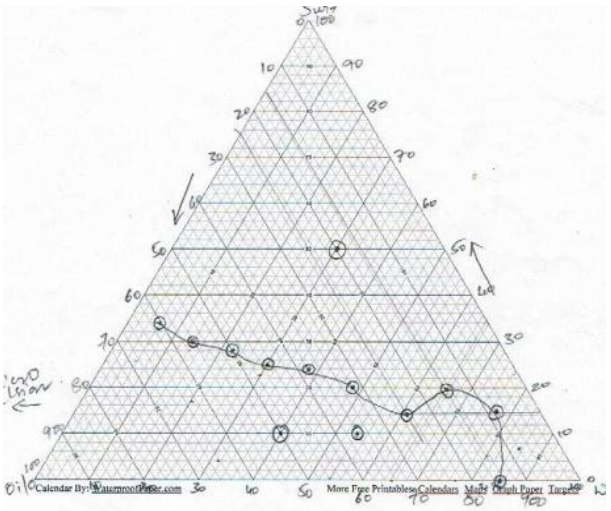

**Fig. 3(a): Ternary phase diagram of 1:1 ratio of Arachis oil: $S_{mix}$ (Tween 80: PEG 400) and water.**

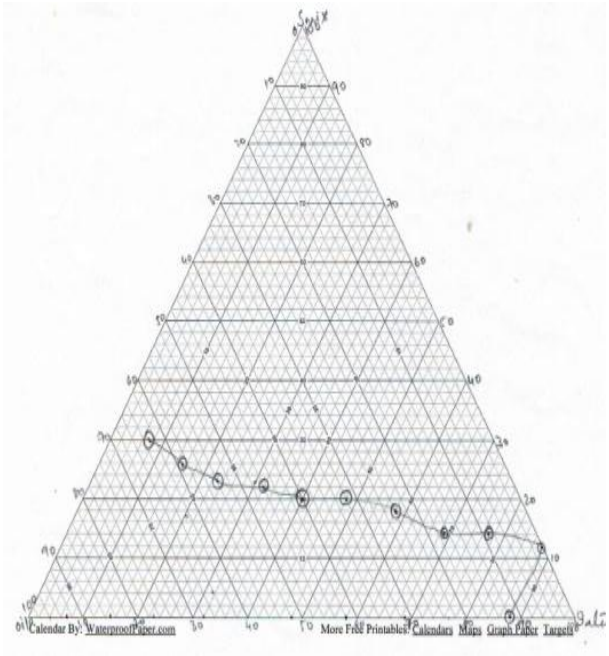

**Fig.3(b): Ternary phase diagram of 1:2 ratio of Arachis oil : $S_{mix}$ (Tween 80:PEG400) and water.**

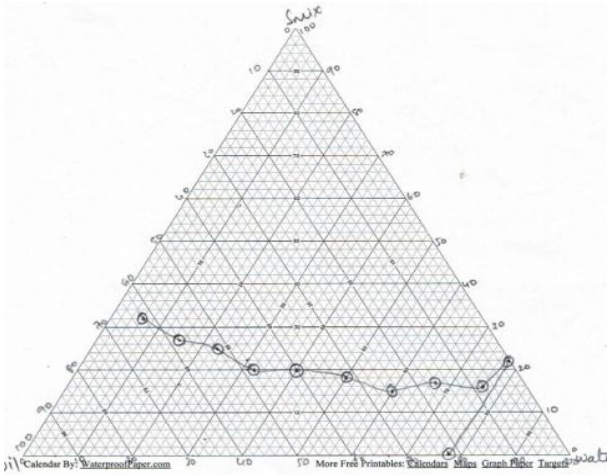

**Fig.3(c) Ternary phase diagram of 1:3 ratio of Arachis oil: $S_{mix}$ (Tween 80:PEG400)and water.**

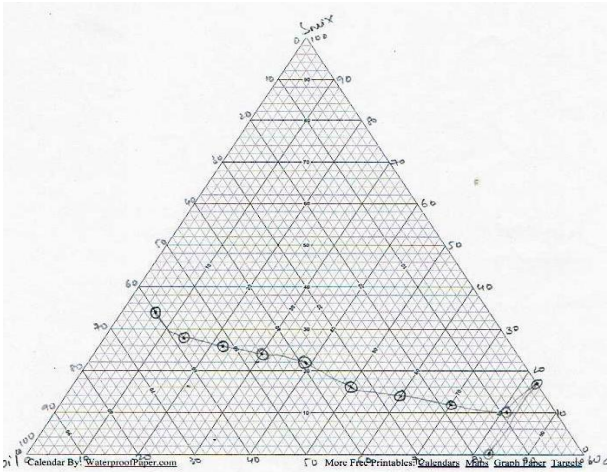

**Fig.3(d): Ternary phase diagram of 2:1 ratio of Arachis oil: $S_{mix}$ (Tween 80:PEG400) and water.**

From the above ternary diagrams, we can select the better emulsification zone for each ratio of S mix without getting the drug precipitated out of each system.

**Characterization of SMEDDS**

**Appearance**

At the end of 24 hrs the emulsions were visually inspected for clarity, phase separation and precipitation of drug.

**Table 4: Assessment of physical compatibility by visual observation of prepared formulation.**

| S No | Formulation | After 24 hours | | |
|---|---|---|---|---|
| | | Phase separation | Precipitation | clarity |
| 1 | A1 | No | No | Not clear |
| 2 | A2 | No | No | Slightly less clear |
| 3 | A3 | No | No | Clear |
| 4 | A4 | No | No | Dull |
| 5 | A5 | No | No | Dull |
| 6 | A6 | No | No | Greyish white |
| 7 | A7 | No | No | Clear |
| 8 | A8 | No | No | Not clear |
| 9 | A9 | No | No | Dull |
| 10 | A10 | No | No | Dull |
| 11 | A11 | No | No | Not clear |
| 12 | A12 | No | No | Less clear |
| 13 | A13 | No | No | Clear |
| 14 | A14 | No | No | Dull |
| 15 | A15 | No | No | Dull |
| 16 | A16 | No | No | Greyish white |
| 17 | A17 | No | No | Slightly less clear |
| 18 | A18 | No | No | Clear |
| 19 | A19 | No | No | Dull |
| 20 | A20 | No | No | Dull |

A3, A7, A13 and A18 were observed to be clear after 24 hrs. Whereas other formulations were either cloudy or opaque in physical appearance.

**Conductance**

Presence of oil in water emulsion formulation was confirmed by measuring conductivity. All SMEDDS are water continuous emulsion systems, some decrease in conductance were due to presence of oil droplets showing resistance to conductance and so decrease in conductance was observed.

**Table 5: Electro conductivity of SMEDDS containing Ezetimibe.**

| S No | Formulation | Conductance | | |
|---|---|---|---|---|
| | | I | II | III |
| 1 | A1 | 47.9 | 47.7 | 47.9 |
| 2 | A2 | 48.2 | 48.2 | 48.3 |
| 3 | A3 | 49.1 | 49.1 | 49.0 |
| 4 | A4 | 47.2 | 47.1 | 47.1 |
| 5 | A5 | 46.4 | 46.5 | 46.3 |
| 6 | A6 | 41.1 | 41.2 | 41.1 |
| 7 | A7 | 49.3 | 49.3 | 49.2 |
| 8 | A8 | 44.2 | 44.7 | 44.8 |
| 9 | A9 | 47.9 | 47.4 | 47.9 |
| 10 | A10 | 46.3 | 46.9 | 46.5 |
| 11 | A11 | 47.1 | 46.9 | 47.0 |
| 12 | A12 | 47.4 | 47.6 | 47.4 |
| 13 | A13 | 49.7 | 49.6 | 49.7 |
| 14 | A14 | 46.9 | 46.9 | 46.7 |
| 15 | A15 | 45.9 | 46.0 | 45.8 |
| 16 | A16 | 48.8 | 48.7 | 48.8 |
| 17 | A17 | 46.9 | 46.4 | 46.6 |
| 18 | A18 | 49.8 | 49.7 | 49.8 |
| 19 | A19 | 47.8 | 47.7 | 47.8 |
| 20 | A20 | 47.2 | 46.9 | 46.9 |

The conductance values for all prepared formulations were ranging from(A1-A20) 40-50, among which among which A3, A7, A13 and A18 were showing higher values of conductance.

**Percentage transmittance**

The clarity of micro emulsions was checked by transparency in terms of percentage transmittance (%T).

**Table 6: Transmittance of SMEDDS containing Ezetimibe.**

| S. No | Formulation | Transmittance (%T) | | |
|---|---|---|---|---|
| | | I | II | III |
| 1 | A1 | 72 | 71 | 72 |
| 2 | A2 | 76 | 74 | 75 |
| 3 | A3 | 84 | 84 | 83 |
| 4 | A4 | 52 | 52 | 51 |
| 5 | A5 | 49 | 49 | 48 |
| 6 | A6 | 73 | 73 | 75 |
| 7 | A7 | 89 | 88 | 88 |
| 8 | A8 | 72 | 74 | 71 |
| 9 | A9 | 52 | 53 | 51 |
| 10 | A10 | 46 | 49 | 42 |
| 11 | A11 | 65 | 65 | 62 |
| 12 | A12 | 71 | 70 | 72 |
| 13 | A13 | 91 | 90 | 91 |
| 14 | A14 | 42 | 39 | 41 |
| 15 | A15 | 37 | 34 | 32 |
| 16 | A16 | 79 | 78 | 76 |
| 17 | A17 | 82 | 84 | 85 |
| 18 | A18 | 98 | 98 | 97 |
| 19 | A19 | 62 | 59 | 57 |
| 20 | A20 | 56 | 52 | 54 |

In the present study the transmittance for all the formulations ranging from (A1-A20) 30-98 and the formulations A3, A7, A13 and A17 were showing higher values.

**Characteristics of solid SMEDDS**

**Drug content**

The drug content of Ezetimibe SMEDDS formulation was measured by using UV-Visible spectroscopic method. (UV-2203, Systronics).

**Table 7: Drug content values of prepared formulations.**

| S. No | Formulation | % Drug content | | |
|---|---|---|---|---|
| | | I | II | III |
| 1 | A1 | 88.4 | 88.7 | 88.6 |
| 2 | A2 | 92.4 | 92.6 | 92.4 |
| 3 | A3 | 98.6 | 98.9 | 98.1 |
| 4 | A4 | 86.9 | 86.5 | 86.7 |
| 5 | A5 | 84.2 | 85.1 | 84.9 |
| 6 | A6 | 86.9 | 86.3 | 86.1 |
| 7 | A7 | 98.3 | 98.2 | 98.7 |
| 8 | A8 | 91.4 | 91.2 | 97.7 |
| 9 | A9 | 83.2 | 83.9 | 83.6 |
| 10 | A10 | 84.6 | 81.9 | 81.7 |
| 11 | A11 | 85.4 | 85.7 | 85.6 |
| 12 | A12 | 91.5 | 91.9 | 92.1 |
| 13 | A13 | 98.6 | 97.4 | 98.3 |
| 14 | A14 | 82.4 | 82.6 | 82.4 |
| 15 | A15 | 80.5 | 81.3 | 81.3 |
| 16 | A16 | 89.5 | 89.9 | 89.1 |
| 17 | A17 | 94.6 | 94.6 | 94.2 |
| 18 | A18 | 98.9 | 98.6 | 98.9 |
| 19 | A19 | 97.4 | 87.4 | 87.6 |
| 20 | A20 | 85.4 | 85.7 | 85.9 |

The drug content values for all prepared formulations were ranging from (A1-A20) 92-99, among which A3, A7, A13, A18 showing high drug content.

**Uniformity of weight of capsule**

Uniformity weight of capsule was determined for all formulations. The value of average weight of capsule range from 525.7-527.5mg. The weight variation was observed within acceptable limit i.e., less then ±7.5% capsule as per IP 2007.

**In vitro dissolution studies**

In vitro dissolution studies have been performed on all formulations (A1-A20) and drug release is observed. Among all A3, A7, A13 and A8 had shown increased drug release when compared with other formulations.

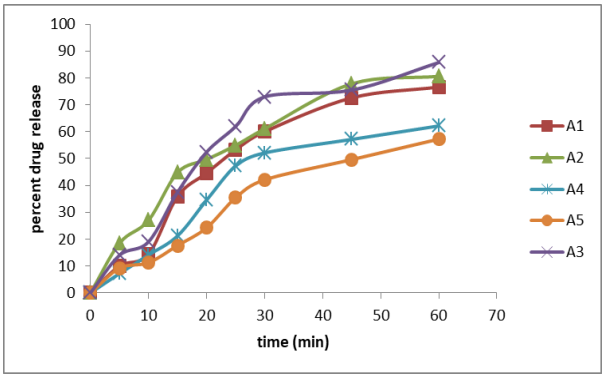


**Fig. 4(a): Dissolution profile of all the prepared SMEDDS (A1-A5) containing Ezetimibe.**

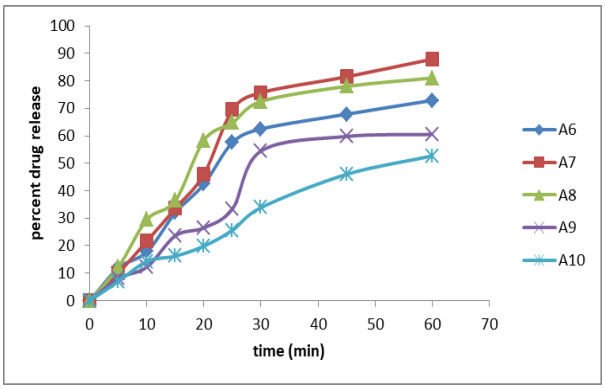


**Fig. 4(b): Dissolution profile of all the prepared SMEDDS (A6-A10) containing Ezetimibe.**

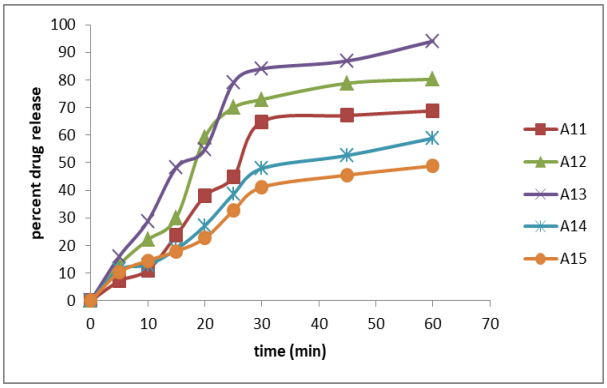


**Fig. 4(c): Dissolution profile of all the prepared SMEDDS (A11-A15) containing Ezetimibe.**

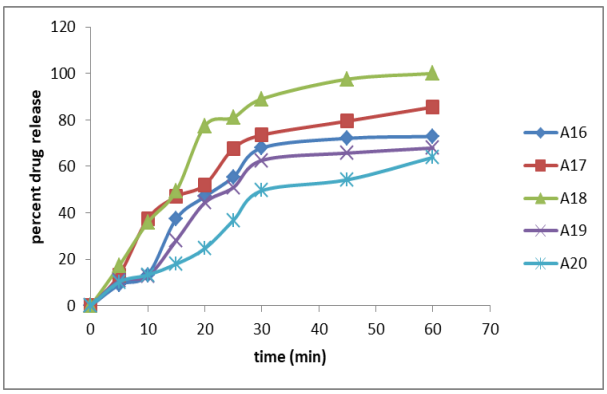


**Fig. 4(d) Dissolution profile of all the prepared SMEDDS (A16-A20) containing Ezetimibe**

The formulation batches A3, A7, A13 and A18 are compared with that of marketed product (Ezedoc®10) and pure drug (Ezetimibe 10 mg) with respect to drug dissolution profile

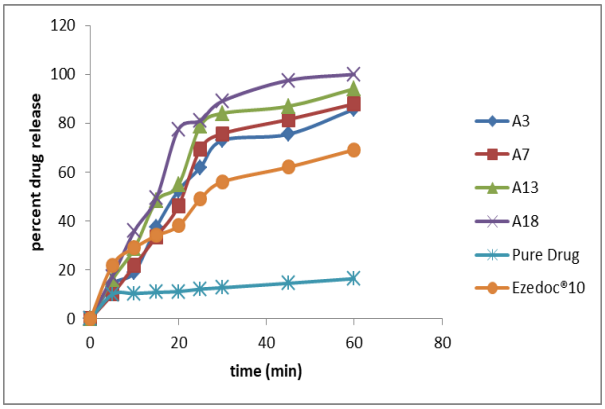


**Fig. 5 Comparison of finalized formulations with marketed preparation and pure drug.**

The formulations A3, A7, A13 and A18 were compared with marketed preparation (Ezedoc®10) and pure drug. The prepared formulations had shown very high dissolution studies than the marketed product and pure drug.

A3, A7, A13 and A18 are found as optimized formulations containing Ezetimibe and further studies are carried out on these formulations.

**Zeta potential**

Zeta potential was performed for all the formulations to determine the potential stability of colloidal systems. Zeta potential was determined by MALVERN zeta sizer instruments and was monitored at 25˚ c at a scattering angle 90˚.

**Table 8: Zeta potential of SMEDDS containing Ezetimibe.**

| S. No | Formulation | Zeta potential (mV) |
|---|---|---|
| 1 | A3 | -14.5 |
| 2 | A7 | -18.5 |
| 3 | A13 | -24.7 |
| 4 | A18 | -26 |

SMEDDS formulation consist of non-ionic components which show relatively neutral charge it means it will not affected by body membrane charge during absorption. Zeta potential performed on all finalized formulations the values are found to be (-14.5mV, -18.5mV, -24.7mV, -26mV).

The droplet size of emulsions which could be determined by a photon correlation spectroscopy using a zetasizer which able to measure sizes between 10 and 500 nm.

**Table 9: Particle size of SMEDDS containing Ezetimibe.**

| S. No | Formulation | Z-Average (nm) |
|---|---|---|
| 1 | A3 | 454.5 |
| 2 | A7 | 345.2 |
| 3 | A13 | 315.2 |
| 4 | A18 | 277.5 |

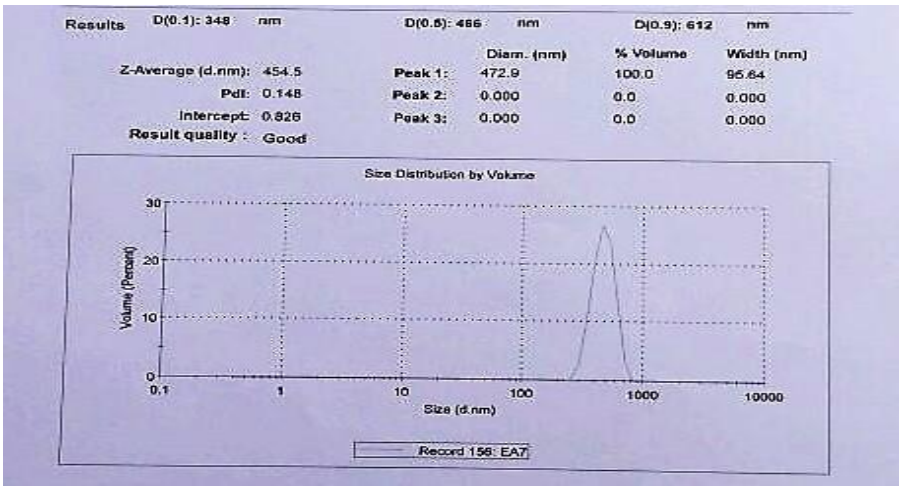


**Fig .6(a): Particle size of SMEDDS (A3) containing Ezetimibe.**

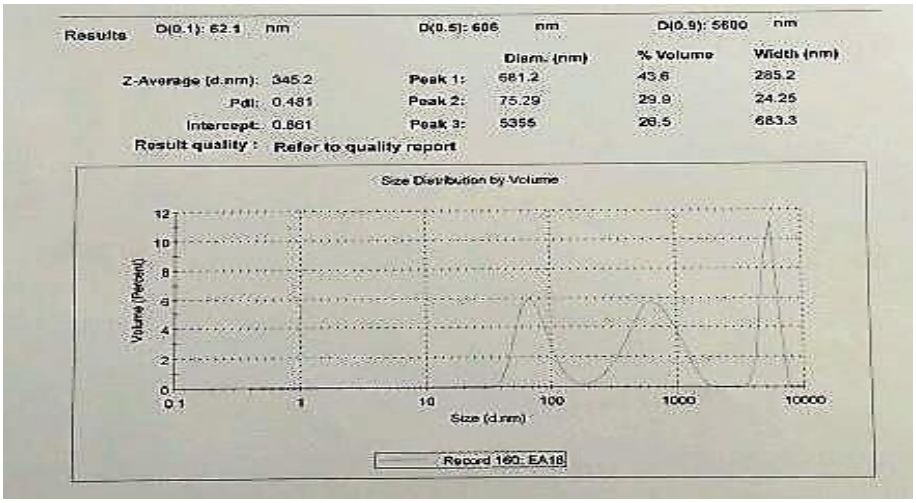


**Fig .6(b): Particle size of SMEDDS (A7) containing Ezetimibe.**

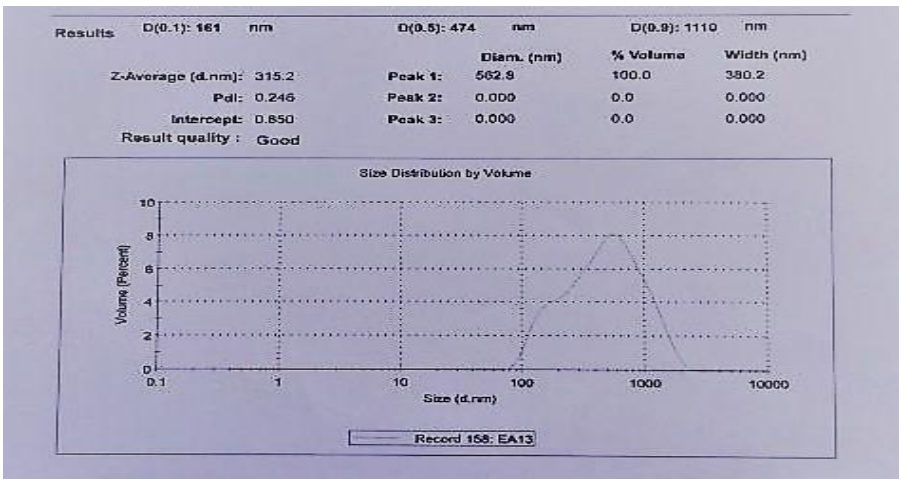


**Fig .6(c): Particle size of SMEDDS (A13) containing Ezetimibe.**

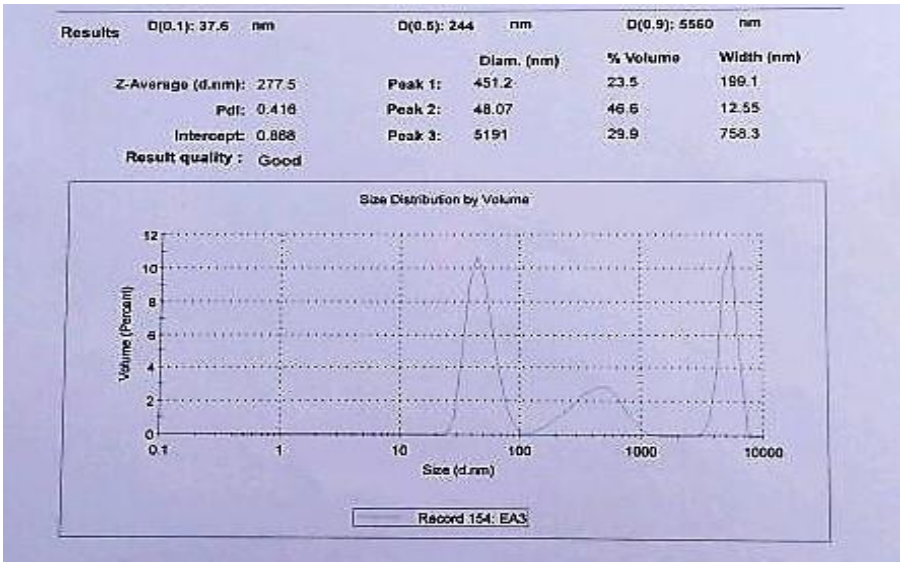


**Fig .6(d) Particle size of SMEDDS (A18) containing Ezetimibe.**

**Stability studies**

Stability studies of the formulations are tabulated below. A18 had shown better stability when compared with other formulations.

**Table 10: Stability studies of SMEDDS.**

| S. No | Formulations | Solubility Studies | |
|---|---|---|---|
| | | Precipitation | Phase seperation |
| 1 | A3 | Yes | No |
| 2 | A7 | Yes | No |
| 3 | A13 | Yes | No |
| 4 | A18 | No | No |

## CONCLUSION

In this study, the SMEDDS of Ezetimibe were prepared using Arachis oil, Tween 80, PEG 400. Based on ternary phase diagrams Tween 80 and PEG400 were selected as surfactant, co-surfactant respectively. The ratios of surfactant, co-surfactant was fixed based on solubility studies. Among all the prepared formulations A3, A7, A13 and A18 were showing better drug content values, %transmittance and conductivity values, further the drug release values also proved that among all the formulations A3, A7, A13 and A18 are showing better profile, these formulations were compared with marketed formulation with respect to drug release data. Hence from all the studies carried out SMEDDS of Ezetimibe can be successfully prepared by using arachis oil, smix (Tween 80: PEG 400) to improve its solubility profile.

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