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Research Article

DEVELOPMENT OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF EZETIMIBE BY SPRAY DRYING TECHNOLOGY: CHARACTERIZATION, IN-VITRO AND IN-VIVO EVALUATION

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ABSTRACT

The present work was aimed at formulating a SMEDDS self-micro emulsifying drug delivery system) of Ezetimibe and evaluating its in vitro and in vivo activity. Ezetimibe belongs to a new class of lipid-lowering agents that selectivity inhibits the intestinal absorption of cholesterol and related plant sterols. Due to very low solubility in the aqueous media ezetimibe shows low bioavailability. The aim of the present study investigation was to develop a Lipid Based Formulation (LBF) to enhance the dissolution as well as the oral bioavailability of practically water insoluble Ezetimibe. Type I & Type IV LBF formulation was prepared and evaluated. Solubility of the drug in different oils, Surfactant & co-surfactant was determined. On the basis of the solubility of the ezetimibe in different oil, surfactant & co-surfactant. Type I & Type IV formulation was prepared in Capriyol 90 (83 mg/ml), Capmul MCM C8 (73.7783 mg/ml) & Cremophor RH 40 (260 mg/ml), Cremophor EL (148 mg/ml), Acysol K 140 (327 mg/ml), Acrysol EL 135 (138 mg/ml), combination of various surfactants with PEG 400. Lipid based formulation then further evaluated for its percentage transmittance, robustness to dilution, stability and drug content. The optimized formulation of Ezetimibe loaded in Lipid based formulation shows complete in vitro drug release in 20min while drug shows only 25.5% drug release in 90 min. *In Vitro* study proved that the potential use of Lipid based formulation improves the dissolution rate of poorly water-soluble drug-Ezetimibe. Comparative pharmacodynamic evaluation was investigated in terms of lipid- lowering efficacy, using a Triton WR 1339-induced hypercholesterolemia model in rats. The SMEDDS formulation significantly reduced serum lipid levels in phases I and II of the Triton WR 1339 test, as compared with plain Ezetimibe. The optimized formulation was then subjected to stability studies as per International Conference on Harmonization (ICH) guidelines and was found to be stable over 12 months. Thus, the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Ezetimibe to improve its bioavailability.

Keywords: Ezetimibe, Lipid-based formulation, Transmission.

INTRODUCTION

Lipid-based drug delivery system [LBDDS] is composed of oil, co-surfactant, surfactant & water miscible organic solvent. The choice of component of the LBDDS varies with type of formulation (oral, injectable, topical, transdermal, pulmonary, ocular) desired and the physicochemical properties of the drug[1-5]. The interest in lipid-based drug delivery system increasing tremendously after their introduction in 1974 by Attwood et al[6]. Increased interest in the LBDDS is because of approximately 40% to 70% of new chemical entities (Drug) developing in the recent days shows inadequate solubility and limited absorption in the GI tract, which reduces the therapeutic concentrations attainable at a given dose of drug[7]. LBDDS have been demonstrated to be useful in enhancing the dissolution rate of the highly lipophilic drug because they can keep the drug in the dissolved state until it is absorbed from GI tract. Lipid-based drug delivery system is of four types, Type I (Oil without surfactant), Type II (Oil with water insoluble surfactant), Type III (Oil, Co-solvent, Surfactant), type IV (water soluble surfactant & co-solvent, no oil)[8-11].

The objective of the present work is to study the effect of lipid-based drug delivery system on the dissolution profile of poorly water-soluble drug (Ezetimibe). Ezetimibe is new class of selective cholesterol absorption inhibitor, which potently inhibits the absorption of biliary and dietary cholesterol from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides or bile acids[12-14]. Ezetimibe is BCS Class II (Low soluble, highly permeable) drug having reported aqueous solubility 0.012 mg/ml[15]. After oral administration, ezetimibe is rapidly absorbed (Within 15 min) and extensively conjugated to a pharmacologically active phenolic glucuronide. Ezetimibe is highly lipophilic drug having the lop P value (octanol/water) 4.5[16,17]. Due to high log P value ezetimibe is hydrophobic in nature and show very low dissolution profile in the gastrointestinal fluid. Its bioavailability is variable as it shows very low dissolution profile. Moreover, the absolute bioavailability of the ezetimibe cannot be determined as it is very low soluble in the water and cannot be injected. Thus, it is very important to increase the dissolution profile of the drug to increase the bioavailability and also to reduce the inter subject variability. Many attempts are done to increase the dissolution profile of ezetimibe, by formulating solid dispersion, nanosuspension, by formulating different polymorph, by combining ezetimibe with different excipient (SLS, microcrystalline cellulose, crosscarmellose etc)[16,18-21]. The present study aims to increase the dissolution profile of the ezetimibe by formulating Type I & Type IV lipid-based drug delivery system (LBDDS). Type I LBDDS is non dispersing system consist of oils without surfactant & type IV LBDDS is dispersing system typically to form a micellar solution which consist of water-soluble surfactant & co-solvent.

MATERIAL AND METHODS

MATERIAL

Ezetimibe was kindly gifted from Ind-Swift Labs, Mohali, India. Acrysol K 140 (polyoxyl 40 hydrogenated castor oil)), Acrysol EL (Polyoxyl 35 castor oil) 135 was gifted by corel pharma chem. Ahmadabad (Gujarat), India. The gift sample of Cremophor RH 40, Cremophor EL was obtained from BASF chemicals, Mumbai (India). Gift sample of Capmul MCM C8, Capmul MCM, Capmul PG 8 NF, Captex 200, Captex 300 were obtained from Abitec Corporation (USA). Capriyol 90 gifted by Gattefosse (France). Triton WR-1339 purchased from Sigma–Aldrich. PEG 400, Methanol & other chemicals of analytical grade was purchased from Modern chemicals, Mumbai.

PREFORMULATION STUDY

Organoleptic Characterization of Drug

Organoleptic characterization of Ezetimibe was done by studying color, odor and appearance and results are shown in given table.

Melting Point

The Melting point of Ezetimibe was done by capillary method.

Solubility

The solubility of Ezetimibe in different solvent such as Distilled water, 0.1N HCl, pH 4.5 phosphate buffer containing 0.15% sodium lauryl sulfate, methanol, and ethanol was determined using shake flask method. An excess amount of Ezetimibe was added in the solvent and vortexing done for 48 hr at room temperature. Mixture was then centrifuge at 3000 rpm for 10 min and filtered through 0.45µm filter paper. Filtrate was further diluted with methanol to obtain suitable concentration. The solubility of ezetimibe was determined by analyzing UV spectra at λmax 232.5nm.

FT-IR Spectroscopy

FT-IR spectra of Ezetimibe was recorded using FT-IR Spectrometer (Jasco 4100, Japan) using KBr pellet technique. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into a transparent disc under high pressure using special dies. The disc was placed in an IR spectrophotometer using a sample holder and spectrum were scanned over wave number range of 4000–400 cm^{-1}.

UV Spectroscopy

Stock solution (10mg/100ml) of Ezetimibe was prepared in methanol. Further dilution of stock solution was prepared to obtain suitable concentration. The UV Spectrum was recorded in the range of 200-400nm on Thermo-fisher UV-2600 double beam spectrometer as shown in Figure1. The wavelength of maximum absorption (λ_{max}) was determined.

Solubility Studies with excipients

The screening of the oil, Surfactant & co-solvent (Co-surfactant) for the formulation of lipid-based formulation was done on the basis of the solubility of the ezetimibe in it. The solubility of the Ezetimibe in different oil, Surfactant & co-surfactant was determined[22]. 3 gm of vehicle and excess amount of drug was added in the vials, the mixture was heated at 40˚C in a water bath to facilitate the solubilization & mixed with the help of mechanical stirrer (glass rod). The mixture was then sonicated for 15 min and then vortexed for about 48 hr at 30^0C. After reaching equilibrium, the mixture then centrifuge for 10 min at 3000 rpm (Remi centrifuge) and supernatant was filtered through membrane filter (0.45 µm whatman, USA) to remove excess amount of drug. The solubility of the ezetimibe in different vehicle was quantified by UV spectrometer (Tharmofishcher 1650) at 231.5nm using methanol as diluents.

PHYSICOCHEMICAL COMPATIBILITY OF EZETIMIBE WITH EXCIPIENT IN LBF

Visual Inspection method

To estimate the physicochemical compatibility of the different excipient used for the present study were done by placing the ezetimibe in combination with the different excipient for 3 months at two different temperatures (RT, 40^0C). The samples were virtually inspected after each 15 days to determine any colour change in the sample.

Fourier transform-infrared spectroscopy

After 3-month IR of all samples were done to determine any incompatibility between the different excipient used for the formulation of lipid-based drug delivery system. FT-IR spectroscopy was performed using FT-IR model Shimadzu 4100, Japan. All the samples diluted by chloroform and FT-IR was taken by using KBr pellet.

Macroscopic Evaluation

Macroscopic evaluation of LBF was carried out to study the stability of the optimized LBF. Any change in the color, transparency or phase separation occurred during normal storage condition (37 ± 2^0C) was observed in optimized lipid formulation.

Transmission test

Stability of optimized lipid-based formulation with respect to dilution was checked by measuring transmittance through UV Spectrophotometer (Themofishcher UV-1650). 1ml LBF was diluted to 100ml with distilled water and transmittance of sample was measured at 231.5nm. For each sample three replicate assays were performed.

Robustness to dilution

Robustness of formulation to dilution was studied by diluting LBF 100 and 300 times with different pH media. 1 ml of LBF was diluted up to 100ml and 300ml with different dissolution media viz. water, 0.1 N HCL, 6.8 phosphate buffer. The diluted LBF formulation were stored for 12 hr and observed for any signs of drug precipitation or phase separation.

FORMULATION OF TYPE I AND TYPE IV LIPID – BASED FORMULATION (LBF)

Different formulation of Type I & Type IV LBF was prepared by using oil, Surfactant and Co-surfactant which solubilize highest amount of ezetimibe in it. All the formulation tabulated contains 500mg vehicle and 10 mg ezetimibe (Table 6).

CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM

Pseudo ternary phase diagram were constructed to investigate the effect of surfactant to co-surfactant ratio (Km) on the area of micro emulsion existence region. It is a well-known fact that the Km value has considerable effect on the area of micro emulsion existence.[25] The lipid mixtures with different surfactant, co surfactant, and oil ratios lead to the formation of SMEDDS with different properties structure. In order to form self-emulsifying o/w and w/o micro emulsions; oil, a blend of two surfactants, and an aqueous phase were used. These four component systems can be best described by pseudo ternary phase diagram where a constant ratio of two of the components was used and other two were varied. To determine optimum concentration of oil, surfactant, and co surfactant, for development of a SMEDDS

formulation, optimum ratios of excipient concentrations established by means of phase diagram studies provided the area of the monophasic region.[26] A pseudo ternary phase diagrams of the investigated quaternary systems Capriyol 90 (oil)/ Capmul MCM C8: PEG 400 (Co-surfactant)/ Acrysol K 140 (Surfactant)/ Water are presented in Figure. Formation of nanoemulsion systems (the shaded area) was observed at room temperature. Phase diagram indicated that Smix ratio 1.5:1 shows larger self-emulsification region than Smix ratio1:1. In the phase diagram there is not any substantial difference between self-emulsification area of Smix 2:1 and Smix 1.5:1. Therefore to avoid the unnecessary use of surfactant with high HLB in the formulation the Smix ratio 3:1 is rejected. It was also observed that in case of Smix 2:1 during water titration there is gel-like mass formation due to the semisolid nature of Acrysol K 140 at room temperature, which requires more vigorous shaking for emulsification to occur, which may not be acceptable for self-emulsification criteria. Based on this, Smix ratio 1.5:1 was selected for further study.[27]

Drug Loading

Phase diagram indicated that Surfactant: Co-surfactant ratio 1.5:1, 2:1 shows larger self-emulsification region than surfactant: co-surfactant ratio 1:1. It was observed that in case of Surfactant : Co-surfactant 2:1 during water titration there is gel-like mass formation which requires more vigorous shaking for emulsification to occur, which may not be acceptable for self-emulsification criteria. Based on this, different formulations with surfactant: co-surfactant ratio 1.5:1 were prepared with the increasing concentration of drug to achieve the highest drug loading in to liquid SMEDDS. The liquid formulation containing Capriyol 90 (oil), Capmul MCM C8: PEG 400 (1:1) (co-surfactant) and Acrysol K 140 (Surfactant) was prepared with the increasing amount of drug to achieve the highest drug loading in to liquid SMEDDS.

Procedure for Liquid SMEDDS Formulation

- Initially weighted accurate quantity of oil and co-surfactant and mix homogenously on magnetic stirrer at 40° C.
- In this warm mixture, drug was added with continuous stirring to form clear solution.
- In the above clear mixture added surfactant and heat at 40-50°C for 10 min to form homogeneous mixture.
- These liquid formulations were then observed visually for 5 days at the interval of 24 hrs for any phase separation.

Development of liquid SMEDDS

The observation from liquid SMEDDS prepared with different drug loading shows that above 2.91% w/w drug loading, drug tends to crystals out upon standing when liquids SMEDDS was diluted to 100 times with water. Hence for further study different formulations containing 2.91%w/w drug were prepared with the varying concentration of oil, surfactant and co-surfactant.

Development of Liquid SMEDDS formulation

Drug loading in liquid SMEDDS formulation shows that maximum 2.91%w/w dug can be loaded in to the SMEDDS formulation. Hence for further study different formulations containing 2.91%w/w drug were selected with the varying concentration of oil, surfactant: co-surfactant (1.5:1). System with highest water absorption capacity was selected for further formulation and also system showing larger micro emulsion region.

CHARACTERIZATION OF LIQUID SMEDDS

Emulsification Efficiency

Emulsifying property of Liquid SMEDDS formulation was determined by diluting SMEDDS formulation 100 times with distilled water, continuously stirring on magnetic stirrer and results are shown in given table**.** Liquid formulation E1 (Capriyol 90- 24.27%w/w, Capmul MCM C8- 14.56%w/w, PEG 400- 14.56%w/w, Acrysol K 140- 43.68 %w/w) form transparent emulsion by forming initially gel like structure with no precipitation when diluted with distill water. Liquid SMEDDS formulation E2 (Capriyol 90- 29.12%w/w, Capmul MCM C8- 13.59%w/w, PEG 400-13.59%w/w, Acrysol K 140- 40.77%w/w) spreads rapidly forming transparent emulsion with no precipitation. Liquid SMEDDS formulation E3 (Capriyol 90- 33.98%w/w, Capmul MCM C8- 12.62%w/w, PEG 400- 12.62%w/w, Acrysol K 140- 37.86%w/w) spreads rapidly forming transparent emulsion with whitish tinge with no precipitation, which give an idea that there are chances of formation of emulsion with a globule size higher than micro range. The study of emulsifying property of different liquid formulation revels that all three formulation shows good emulsifying property.

Precipitation Assessment

The formulated SMEDDS diluted with the 100 ml purified water and the diluted SMEDDS observed for the precipitation and result was shown in given table. Diluted Liquid SMEDDS E1, E2 formulation form the clear transparent emulsion with no precipitation after 24 hr while E3 formulation form clear transparent emulsion with precipitation after 24hr. The results of precipitation study show that E3 formulation shows precipitation after 24hr, so this formulation is not suitable for the formulation of Micro-emulsion while Formulation E1 and E2 form stable emulsion, so these formulations (E1 and E2) are selected for further characterization.

Measurement of mean globule size

The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. Globule size of Liquid SMEDDS E1 and E2 formulation was found to be 74.31nm and 162.71nm respectively. The result of globule size analysis data revels that globule size of the Liquid SMEDDS formulation is inversely proportional to surfactant concentration. The globule size decreases as the surfactant concentration in the SMEDDS formulation increases. The E2 formulation showed higher globule size because in E2 formulation Smix (Surfactant: Co-surfactant) content is low as compare to E1 formulation. The globule size distribution and polydispersity index revealed that, E1 and E2 formulation shows the closer globule size distribution and also produces the finest emulsion. But in the case of E1 formulation due to higher concentration of surfactant (Acrysol K 140) the viscosity of the formulation is higher as compared to E2 formulation which produces difficulty during the formulation. Also, in E1 formulation because of the disproportionate content of oil/Smix (Surfactant: Co-surfactant) to form a stable system, there is a problem of slow drug loading. Therefore, from the collective experimental observation the formulation E2 is considered to be a good formulation.

SOLID STATE CHARACTERIZATION OF S-SMEDDS POWDER

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) of Ezetimibe and Solid-SMEDDS was performed and result is shown in given figure. DSC of Ezetimibe exhibited sharp melting endotherm at 165.51^0C with onset at 164.02^0C and recovery at 168.26^0C. The DSC of S-SMEDDS shows not show any sharp melting peck of Ezetimibe. The absence of sharp melting peck of ezetimibe in the range of $165\text{-}168^0$C in the DSC of S-SMEDDS indicate that the lipids and Aerosil 20 inhibited the crystallization of Ezetimibe i.e.

ezetimibe is in amorphous form or in solubilized form in S-SMEDDS.

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to determine the particle morphology of pure drug and optimized SMEDDS. The Scanning electron microscopy of Ezetimibe, Aerosil 200 and Solid-SMEDDS was done and results are shown in given figure. Figure revealed that ezetimibe presents as crystalline powder with rectangular plate shaped crystals. Aerosil 200 (Colloidal silicon dioxide) was detected as aggregates of amorphous particles. The Solid-SMEDDS shows irregular shaped granular particle. SEM of the Solid-SMEDDS does not show any rectangular crystals of drug (Ezetimibe) on the surface of aerosil 200 indicate that drug is present in the soluble form in lipid (SMEDDS formulation), which is adsorbed on the surface of aerosil 200.

Powder X-ray Diffraction

The X-ray diffraction patterns of ezetimibe, Colloidal silicon dioxide, physical mixture of ezetimibe and colloidal silicon dioxide and Solid-SMEDDS was done and shown in given figure. In the X-ray diffraction pattern of ezetimibe, the sharp peaks at a diffraction angle 2Ɵ of 8.32º, 13.93º, 18.70º, 19.14º, 19.43º, 20.27º, 20.93º, 22.48º, 23.67º, 24.02º, 25.68º and 29.80º are present. The sharp diffraction peaks of ezetimibe were still detectable in physical mixture with Aerosil 200. X-ray Diffraction patterns of Solid-SMEDDS were characterized by diffuse spectra and no characteristic peaks of ezetimibe were observed. Presence of sharp X-ray diffraction peaks of ezetimibe in physical mixture of ezetimibe and Aerosil 200 and absence of sharp X-ray diffraction peaks of ezetimibe in the Solid-SMEDDS formulation reveals that drug (Ezetimibe) either present in the amorphous form or present in solubilized form in Solid-SMEDDS.

Stability

Temperature Stability

Shelf life is function of time and storage temperature. Temperature stability of the LBF was evaluated by visual inspection of the LBF at different time period. LBF was diluted with purified distilled water. To check the temperature stability of the optimized LBF, they were placed at different temperature range- Freeze temperature (2-8ºC) and Room temperature (25-35ºC). The formulation then observed for any sign of phase separation, flocculation or precipitation.

Centrifugation

To determine the stability of the metastable LBF system, the optimized LBF was diluted with doubled distilled water. The diluted LBF then centrifuged at 1000 rpm for 15 min at 37^0 C and observed for any change in the homogeneity of diluted LBF formulation.

***In-Vitro* release Study**

In vitro release profile of the pure drug (Ezetimibe) and LBF was determined by the use of the USP I (basket) apparatus. Pure drug and LBF equivalent to 10 mg was filled in the hard gelatin capsule having size "0". The capsule then separately placed in the basket containing 450 ml of pH 4.5 phosphate buffers and 0.15% Sodium lauryl sulphate (SLS) maintained at 37 ± 1^0 C with 50 rpm rotating speed[23]. 5ml sample were withdraw after regular time interval (5, 10, 20, 30….120 min) and filter through the whatman filter paper (0.45µm filter). To maintain the sink condition an equal quantity (5ml) of dissolution media was added. The drug release was determined by UV Spectrophotometer (Themofisher UV-1650) at 231.5nm.

Statistical Analysis

The US FDA guidance for industry on dissolution testing of immediate release (IR) solid oral dosage forms (1997) and bioavailability and bioequivalence study guidance for oral dosage forms, describes the model independent mathematical approach proposed by Moore and Flanner for calculating a dissimilarity factor f_1 and a similarity factor f_2 of dissolution across a suitable time interval[24]. The similarity factor f_2 is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by following equation

$$f_2 = 50 \log\{ [1 + \frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2]^{-0.5} \text{ x } 100\}$$

Where n is the number of withdrawal points, R_t is the percentage dissolved of reference at the time point t (marketed product of Ezetimibe) and T_t is the percentage dissolved of test at the time point t (Lipid based formulation). A value of 100% for the similarity factor ($f2$) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles.

Estimation of Drug Content

Drug content of optimized LBF was determined by extracting the LBF with the methanol using the sonication technique. The drug content in the methanolic extract was determined by UV Spectrophotometer (UV-1650 Themofisher) at 231.5nm after suitable dilution.

Solubility Study

The solubility study of the drug was done in the oil, Surfactant and Co-surfactant.

Screening of oil

The objective of determining the solubility of ezetimibe in different oil was to screen the oil phase to development of ezetimibe type I LBF among the different oil. The oil having highest solubility of ezetimibe was selected for the development of the LBF. Solubility of the ezetimibe in different oil was determined in triplicate manner in different oils were shown in figure1. Among the different oil Capriyol 90 (83mg/ml), Capmul MCM C8 (73.77mg/ml), Capmul PG 8 NF (70mg/ml) Shows highest solubility for ezetimibe and due to this they selected to formulation of Type I LBF.

Screening of Surfactant

Non-ionic surfactant is most commonly used for the formulation of the lipid based formulation due to its less toxic nature as compare with the ionic surfactant (anionic & cationic). As non-ionic surfactants are less toxic, they are usually accepted for oral administration. In the present study surfactants (Acrysol EL 135, Acrysol K 140, Cremophor EL, Cremophor RH 40, Span 20, Span 80, Tween 20, Tween 80) were selected to determine the solubility of the ezetimibe. From the different surfactant Acrysol EL (138mg/ml), Acrysol K 140 (327 mg/ml), Cremophor EL (148 mg/ml), Cremophor RH 40 (260 mg/ml) shows highest solubility as compare with the other surfactant. As they show highest solubility for ezetimibe, they are selected for the formulation of lipid-based drug delivery system. The solubility of the drug in different surfactant was determined in the triplicate manner.

Screening of Co-surfactant (Co-solvent)

Co-surfactants are used mainly in combination with the surfactant to formulate the Type IV LBF. Co-surfactants are used as an adjunct to surfactant for increase the dissolution of the drug. Co-surfactant improves the dispersibility drug in LBF. For the

present study three surfactant (Polyethylene glycol, Propylene glycol, Acconon® MC- 8 are used to determine the solubility of the drug. Out of two co-surfactants poly ethylene glycol (410 mg/ml) show highest solubility for ezetimibe. So it was selected for further study. The solubility of the drug in different co-surfactant was determined in the triplicate manner.

PHYSICOCHEMICAL COMPATIBILITY OF EZETIMIBE TO EXCIPIENT

Visual Inspection

The visual inspections of ezetimibe in combination of different lipid vehicle were done for three months. The Visual inspections shows that there was no interaction i.e. colour change, odour observed for 3 months.

Fourier transform-infrared spectroscopy

FT-IR of Ezetimibe and E_1, E_2, E_3, E_4, E_5, E_6, E_7, E_8, E_9, E_{10}, E_{11} was shown in the figure 4(a), 4(b), 4(c). FT-IR of pure drug and different LBF showing characterize IR absorption peaks at 3271 cm^{-1} (Broad, intermolecular hydrogen bonded, O-H stretch), 3022 cm^{-1} (Aromatic C-H stretch), 2962 cm^{-1} (Aliphatic C-H stretch), 1890 cm^{-1} (weak combination and overtone band of ring), 1720 cm^{-1} (C=O of lactam), 1602 cm^{-1} (ring skeletal vibration band), 1504 cm^{-1} (ring C=C Stretch), 1444 and 1433 cm^{-1} (C-N stretch), 1371 cm^{-1} (in plane O-H bend), 1220 cm−1 (C–F stretch), 1066 cm^{-1} (C-O stretch of secondary alcohol) and 815 cm^{-1} (ring vibration due to paradisubstituted benzene). No change in the absorption peaks of functional group of ezetimibe was observed. This shows that ezetimibe is stable with all lipids which used in this study.

Transmission test

Transmission test of LBF was done by the diluting the LBF 100 times with different media such as 0.1 N HCl, 6.8 Phosphate buffer, Distilled water and then analyzing the sample at 650 nm using UV spectrophotometer. As Type I and Type IV LBF contain only oil and surfactant respectively, they do not show the 100 % transparency as the micro-emulsion and nanoemulsion (Type III) shows. From the transparency Type IV LBF containing only surfactant shows more transparency as compare to Type I LBF containing only oil. Type IV LBF containing surfactant and co-surfactant shows highest transparency as compared with the Type I and Type IV LBF containing only oil and surfactant respectively. Acrysol EL 135 and Cremophor EL in combination with PEG 400 (1:1) ratio show highest transparency as compared with other LBF formulation.

Robustness to dilution

Diluted LBF with the different type of media does not show any drug precipitation or phase separation when stored for 24 hr. No change in the diluted LBF on storage, it reveals that all LBF are robust to dilution.

Stability Study

Stability study of LBF formulation was done by studying the effect of different storage temperature and centrifugation on LBF. The temperature stability study of the LBF was done by keeping the sample for three months at two different temperature (Freeze temp. 2-8 ^{0} C and Room Temp.). The samples are virtually inspected after each 15 days, to check any drug precipitation, phase separation or any change in the LBF formulation. The results of visual observation are shown in table 3. Except E_3, all other LBF does not show any change during stability study for 3 months. This indicate that all LBF formulation (Except E_3) were stable at both freeze and room temperature.

After 3-month LBF sample was centrifuged at 3000 rpm for 15 min and the observed results were shown in table 4. Capmul PG 8 NF containing LBF showing drug precipitation after the centrifugation for 15 min and all other LBF were found to be stable.

IN-VITRO RELEASE STUDY OF EZETIMIBE

Dissolution of the pure drug (ezetimibe) and all LBF formulation were done in the pH 4.5 buffer, 0.15 % Sodium lauryl Sulphate. In-vitro drug release pattern of the pure drug and LBF was shown in figure 6(a), 6(b), 6(c). The drug release pattern of the pure drug and LBF formulation shows that Type I and Type IV LBF shows faster in-vitro drug release as compared with the pure drug. In Type I LBF E_2 formulation show fastest drug release than the pure drug and others Type I LBF. From in-vitro study it was observed that E_8 (Type IV LBF) LBF shows fastest drug release as compare with other type IV LBF formulation. This indicates that LBF containing surfactant and co-surfactant shows fastest drug release than all other LBF containing only oil and surfactant singly.

From in-vitro drug release data shows that drug release pattern (drug dissolution rate) increases by the formulating the Lipid based formulation of pure drug. As dissolution rate increases, the bioavailability o the drug also increases. It was confirmed that by formulating LBF of ezetimibe bioavailability can be increases.

The value of f_2 (similarity) near about 100 indicate the 100% similarity of in-vitro dissolution profile of drug and LBF. The f_2 value less than 50 shows dissimilarity of in-vitro dissolution profile of the drug and LBF. All the similarity factor of LBF with pure drug was shown in table 8. Very small value of f_2 (<50) similarity factor indicate that the in-vitro dissolution profile of LBF were dissimilar than dissolution profile of drug.

LIPID-LOWERING STUDIES

The study was performed to evaluate the pharmacodynamic potential of a Final Ezetimibe formulation against plain Ezetimibe using a Triton WR 1339-induced hyperlipidemia model. Triton WR 1339 is a nonionic surfactant that induces hyperlipidemia by inhibiting peripheral lipoprotein lipase enzymes responsible for removal of lipid particles from the body. The administration of Triton WR 1339 leads to transient elevation of lipid levels, which reach a peak at 18 to 24 hours after administration (phase I) and start to lower again the following day (phase II). This experimental model has been previously used for screening the activity of the antilipidemic agent benzafibrate (a fibric acid derivative). Thus, for our present study this method was used to evaluate the lipid-lowering activity of the developed formulation. The precise mechanism by which Ezetimibe exerts its antihyperlipidemic effect has not been clearly established. It was observed that Ezetimibe and its formulation were found to affect the serum lipid level in both phase I and phase II. Table 14 gives the effect of treatments on serum lipid levels in phase I (24 hours). Ezetimibe produced a fall in serum cholesterol (53.20% inhibition), triglyceride (65.50% inhibition), and LDL (58.59% inhibition). The SMEDDS formulation, as expected, performed better than Ezetimibe, resulting in a significant reduction of serum cholesterol (89.89% inhibition), triglycerides (91.30% inhibition), and LDL levels (92.30% inhibition). It has been reported that there is a natural tapering in cholesterol and triglyceride values in phase II of the Triton WR 1339 test. However, this normal clearance of serum lipid in phase II of the Triton WR 1339 test can also be triggered by the presence of a drug in the circulation. Ezetimibe is known to have a longer stay in the blood circulation, as it has a biological half-life of 22 hours. Thus, a longer duration of action is guaranteed provided that there is an optimal initial plasma drug level, which is generally determined by the bioavailability of the drug. We also evaluated the effect of Ezetimibe and the SMEDDS formulation in phase II

of the Triton WR 1339 test. As seen from Table 14, plain Ezetimibe lowered cholesterol (43.80% inhibition), triglyceride (68.50% inhibition), and LDL (55.42% inhibition). The SMEDDS formulation resulted in a greater reduction of cholesterol (96.52% inhibition), triglyceride (95.42% inhibition), and LDL (98.21% inhibition). Thus, the higher lipid-lowering activity of the SMEDDS formulation in both phase I and phase II of the Triton WR 1339 test can be explained by the fact that the SMEDDS formulation resulted in complete dissolution of Ezetimibe, which could have increased absorption and thereby led to a higher plasma drug concentration (higher bioavailability). The low bioavailability of Ezetimibe is attributed to its poor aqueous solubility. The above difference in pharmacodynamic activity and the results from in vitro dissolution studies thus suggest that the SMEDDS formulation resulted in higher oral bioavailability owing to higher solubilization of Ezetimibe from the SMEDDS formulation as compared with plain Ezetimibe.

Estimation of Drug Content

Drug content of all LBF formulation was determined. The drug content of the formulations was tabulated in table 5

Table 1: Organoleptic Properties of Drug

Sr. No.	Parameter	Observation
1	Colour	White or colorless
2	Odor	Odorless
3	Appearance	Solid, Amorphous Powder

Table 2: Solubility data of Ezetimibe in different solvent

Sr. No.	Solvent	Solubility(mg/mL) at 23^{0}C
1	Water	0.012
2	0.1 N HCl	0.011
3	pH 4.5 phosphate buffer (0.05M) with 1% sodium lauryl sulfate	0.16
4	pH 4.5 acetate buffer (0.05M) with 0.45% sodium lauryl sulfate	0.054
5	Methanol	> 200
6	Acetone	> 200
7	DMSO	> 200

Table 3: Parameters for the calibration curve of Ezetimibe

Sr. No.	Parameter	Range
1	Drug	Ezetimibe
2	Concentration of Stock Solution	100µg/ml
3	Absorption Maximum	231.5 nm.
4	Solvent	pH 4.5 phosphate buffer containing 0.15% SLS
5	Scanning Range	200-400 nm.
6	Instrument	Thermo-fisher UV-2600 Spectrophotometer
7	Sample holder	Quartz

Table 4: Drug Loading in Liquid SMEDDS Formulation

Sr. No.	Ingredients	Quantity in %w/w			
		D1	D2	D3	D4
1	Drug (Ezetimibe)	0.99	1.96	2.91	3.84
2	Capriyol 90	24.72	24.50	24.27	24.03
3	Capmul MCM C8	14.85	14.70	14.56	14.42
4	PEG 400	14.85	14.70	14.56	14.42
5	Acrysol K 140	44.55	44.11	43.68	43.26
	% Total	100	100	100	100

Table 5: Liquid SMEDDS Formulation

Sr. No.	Ingredients	Quantity in %w/w		
		E1	E2	E3
1	Drug (Ezetimibe)	2.91	2.91	2.91
2	Capriyol 90	24.27	29.12	33.98
3	Capmul MCM C8	14.56	13.59	12.62
4	PEG 400	14.56	13.59	12.62
5	Acrysol K 140	43.68	40.77	37.86
	% Total	100	100	100

Table 6: Different formulation of Type I and Type IV LBF.

Formulation	Batch	Ingredient
Type I	E_1	Capriyol 90+ Ezetimibe
Type I	E_2	Capmul MCM C 8+ Ezetimibe
Type I	E_3	Capmul PG 8 NF+ Ezetimibe
Type IV	E_4	Cremophor EL+ Ezetimibe
Type IV	E_5	Cremophor RH 40+ Ezetimibe
Type IV	E_6	Acrysol EL 135+ Ezetimibe
Type IV	E_7	Acrysol K 140+ Ezetimibe
Type IV	E_8	Cremophor EL: PEG 400 (1:1) + Ezetimibe
Type IV	E_9	Cremophor RH 40: PEG 400(1:1) + Ezetimibe
Type IV	E_{10}	Acrysol EL135: PEG 400(1:1) + Ezetimibe
Type IV	E_{11}	Acrysol K 140: PEG 400(1:1) + Ezetimibe

Table 7: Visual assessment of Liquid SNEDDS

Sr.No.	Formulation Code	Speed of Emulsification	Clarity
1	E1	Instant	Formulation formed transparent, gel like intermediate structure prior to form emulsion
2	E2	Instant	Formulation spreads rapidly in water forming clear and transparent emulsion
3	E3	Instant	Formulation spreads rapidly in water forming transparent emulsion with white ting like structure

Table 8: Precipitation assessment of different Liquid SMEDDS formulation

Sr.No.	Formulation Code	Precipitation after 24 hrs, stability
1	E1	Transparent, Clear emulsion, No precipitation, Stable
2	E2	Transparent, Clear emulsion, No precipitation, Stable
3	E3	Transparent, Clear emulsion, with precipitation after 24 hr

Table 9: Globule size distribution and polydispersity index of liquid SNEDDS

Sr.No.	Formulation Code	Globule Size (nm)	Polydispersity Index (PDI)
1	E1	114.31	0.331
2	E2	162.71	0.362

Table 10: % transmittance of various LBF, upon 100, 300 times dilution with water, 0.1N HCL, 6.8 buffer.

Batch	Transmittance (%) ± S.D.					
	100 times dilution with water	300 times dilution with water	100 times dilution with 0.1 N HCL	300 times dilution with 0.1 N HCL	100 times dilution with 6.8 Buffer	300 times dilution with 6.8 Buffer
E_1	27.71±0.002	31.63±0.001	25.13±0.004	32.13±0.001	28.19±0.004	36.83±0.002
E_2	34.43±0.005	39.87±0.001	32.64±0.002	37.79±0.003	36.83±0.006	39.57±0.005
E_3	51.28±0.003	57.58±0.002	50.01±0.005	56.18±0.006	53.58±0.002	58.88±0.002
E_4	91.90±0.003	93.17±0.004	89.73±0.001	91.43±0.005	92.01±0.003	93.08±0.003
E_5	87.14±0.004	88.91±0.004	85.28±0.004	87.01±0.002	87.37±0.004	89.82±0.004
E_6	90.32±0.002	92.23±0.004	87.97±0.002	90.97±0.003	92.45±0.001	93.19±0.002
E_7	88.53±0.001	90.31±0.002	86.78±0.004	88.71±0.006	89.36±0.002	91.71±0.001
E_8	97.49±0.004	98.14±0.004	94.99±0.006	96.36±0.002	97.09±0.004	98.91±0.003
E_9	93.21±0.005	94.45±0.003	91.19±0.004	92.75±0.004	94.11±0.001	95.15±0.006
E_{10}	96.15±0.004	97.43±0.005	95.85±0.005	96.15±0.006	96.78±0.003	98.13±0.001
E_{11}	94.18±0.003	96.17±0.006	93.58±0.006	94.62±0.004	95.26±0.004	96.87±0.005

Table 11: Temperature stability study of various LBF for different time interval

Batch	Phase separation, Flocculation, Drug Precipitation					
	After 1 month		After 2 months		After 3 months	
	Freeze	RT	Freeze	RT	Freeze	RT
E_1	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_2	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_3	Not seen	Not seen	seen	seen	seen	seen
E_4	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_5	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_6	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_7	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_8	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_9	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_{10}	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen
E_{11}	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen

Table 12: Centrifugation stability study of various LBF for different time interval.

Batch	Phase Separation		
	After 1 month	After 2 months	After 3 months
E_1	Not seen	Not seen	Not seen
E_2	Not seen	Not seen	Not seen
E_3	Not seen	seen	seen
E_4	Not seen	Not seen	Not seen
E_5	Not seen	Not seen	Not seen
E_6	Not seen	Not seen	Not seen
E_7	Not seen	Not seen	Not seen
E_8	Not seen	Not seen	Not seen
E_9	Not seen	Not seen	Not seen
E_{10}	Not seen	Not seen	Not seen
E_{11}	Not seen	Not seen	Not seen

Table 13: Similarity factor (f2) and Drug content of Various LBF

Sr. no.	Batch	Similarity factor (f_2)	Drug content
1	E_1	49.01	97.3±1
2	E_2	32.78	96.4±1
3	E_3	39.06	93.4±1
4	E_4	29.94	97.3±1
5	E_5	39.32	95±1
6	E_6	30.85	96.2±1
7	E_7	37.59	95.2±1
8	E_8	28.16	99.1±1
9	E_9	29.41	96.5±1
10	E_{10}	27.85	98.7±1
11	E_{11}	32.31	96.2±1

Table 14: Effect of Treatment on Serum Lipids in Phase I and Phase II of Triton WR 1339 Test*

PHASE I						
Treatment Group (n = 6)	Cholesterol (mg/dL)	Cholesterol (% inh)	Triglycerides (mg/mL)	Triglycerides (% inh)	LDL (mg/mL)	LDL (% inh)
Control group	57.7 ± 12.2	-	54.6 ± 9.8	-	33.1 ± 12.4	-
Triton WR 1339	161 ± 12.1	-	219 ± 25.5	-	176 ± 9.9	-
Placebo	169 ± 11.8	-	221 ± 22.1	-	179 ± 8.8	-
Plain drug	105 ± 4.6 †	53.2	111 ± 9.1 †	65.5	87.6 ± 3.3‡	58.59
SMEDDS	63.9 ± 5.3 ‡	89.89	69.2 ± 8.2§	91.3	41.3 ± 5.1 ‡	92.30

PHASE II						
Treatment Group (n = 6)	Cholesterol (mg/dL)	Cholesterol (% inh)	Triglycerides (mg/mL)	Triglycerides (% inh)	LDL (mg/mL)	LDL (% inh)
Control group	56.2 ± 10.1	-	58.2 ± 10.1	-	27.9 ± 9.7	-
Triton WR 1339	103 ± 4.3	-	113 ± 4.12	-	91.2 ± 5.3	-
Placebo	105 ± 7.1	-	115 ± 3.01	-	95.8 ± 4.6	-
Plain drug	85.1 ± 2.8 †	43.8	73.5 ± 4.6†	68.50	57.3 ± 2.2 ‡	55.42
SMEDDS	53.5 ± 7.2 ‡	96.52	61.5 ± 7.2§	95.42	31.2 ± 6.1 ‡	98.21

*Data presented as mean ±SD. statistically significant difference between treated group and control group. LDL indicates low-density lipoprotein; SMEDDS, self-microemulsifying drug delivery system.
† P < .05, ‡ P < .01, § P < .001

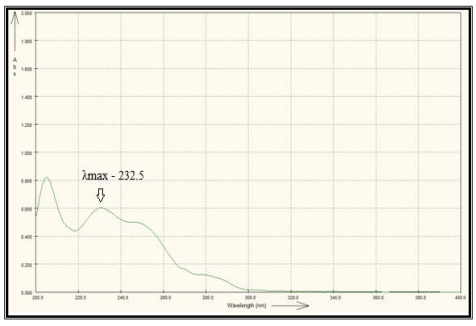

Figure 1: UV- Spectra of Ezetimibe in methanol solvent

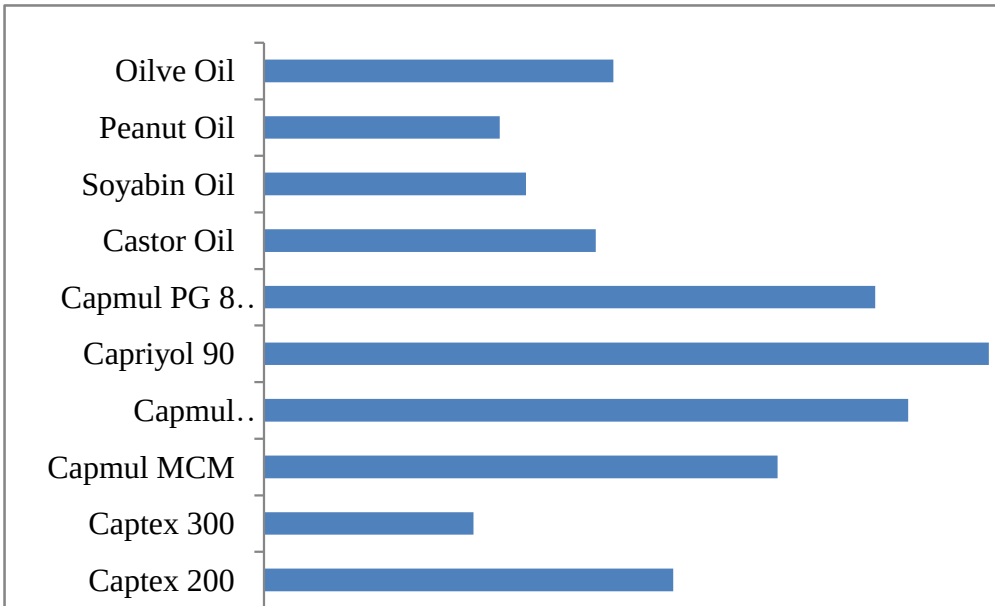

Figure 2: Solubility Study of ezetimibe in various oils.

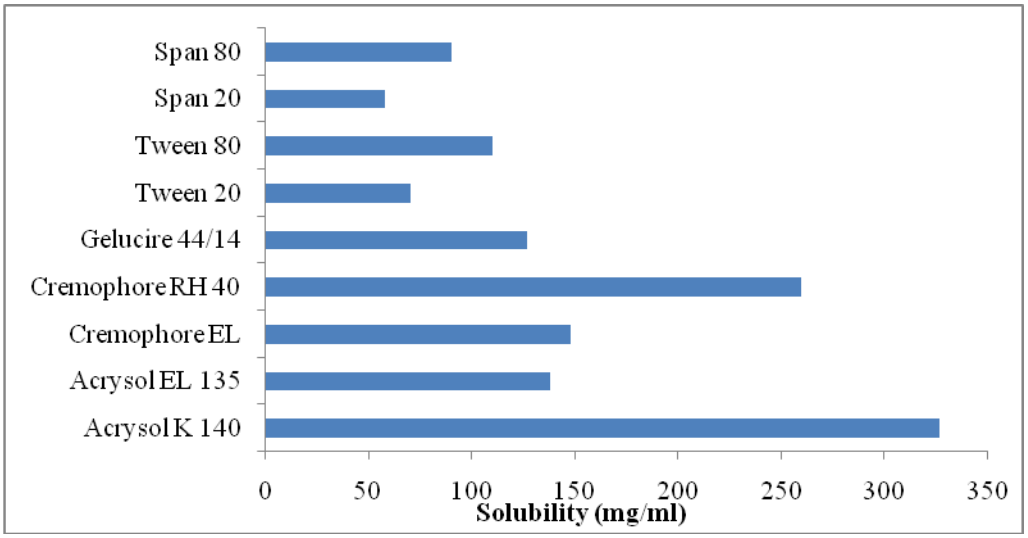

Figure 3: Solubility Study of ezetimibe in various surfactants.

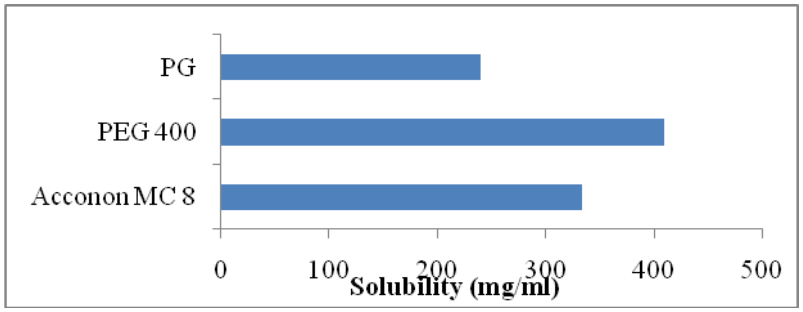

Figure 4: Solubility Study of ezetimibe in various Co-Surfactants.

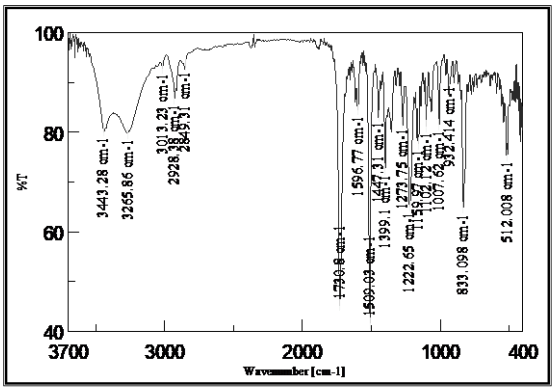

Figure 5: FT-IR of Ezetimibe

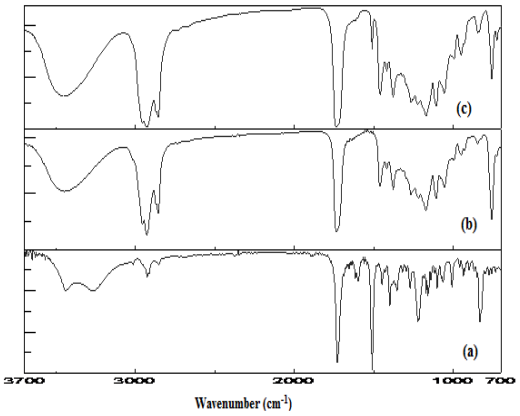

Figure 6: FT-IR of (a) Ezetimibe, (b) Capriyol 90, (c) Ezetimibe + Capriyol 90

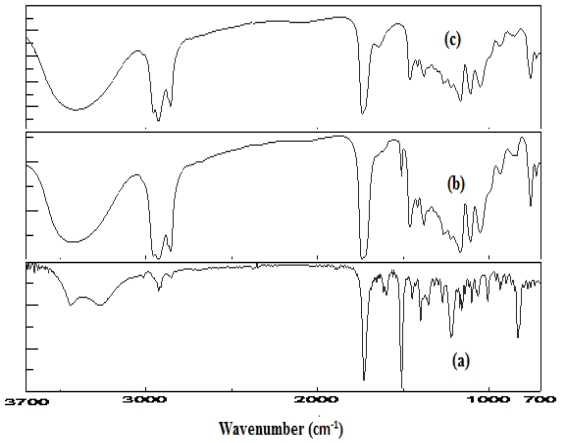

Figure 7: FT-IR of (a) Ezetimibe, (b) Capmul MCM C8, (c) Ezetimibe + Capmul MCM C8

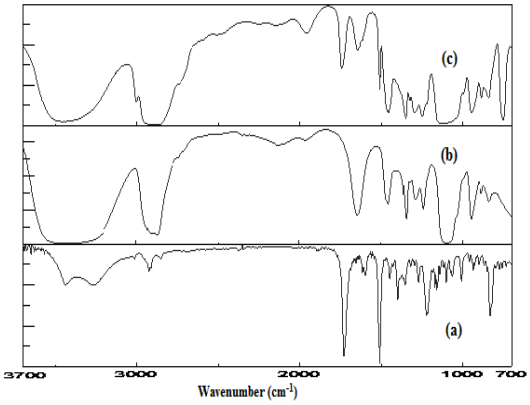

Figure 8: FT-IR of (a) Ezetimibe, (b) PEG 400, (c) Ezetimibe + PEG 400

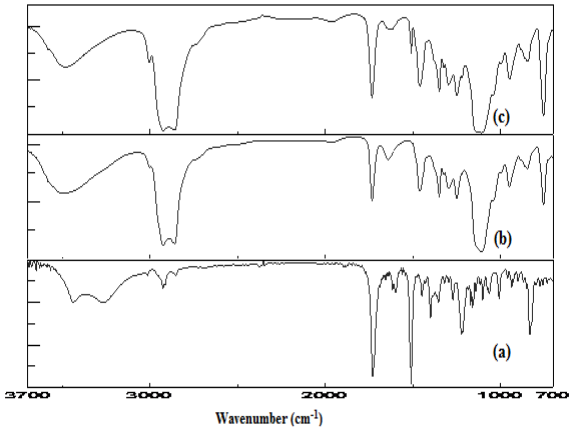

Figure 9: FT-IR of (a) Ezetimibe, (b) Acrysol K 140, (c) Ezetimibe + Acrysol K 140

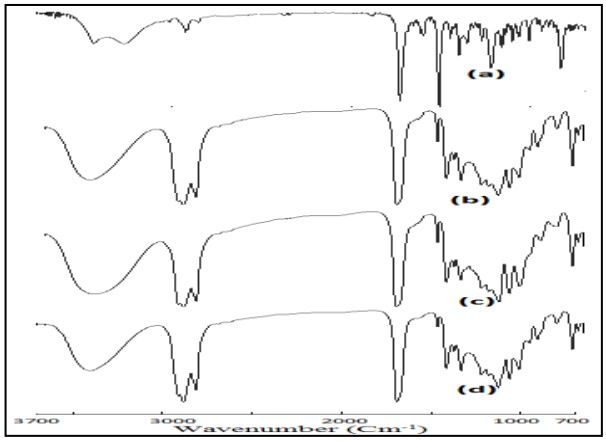

Figure 10(A): FT-IR of (a) Ezetimibe (EZT) (b) E1 (c) E2 (d) E3.

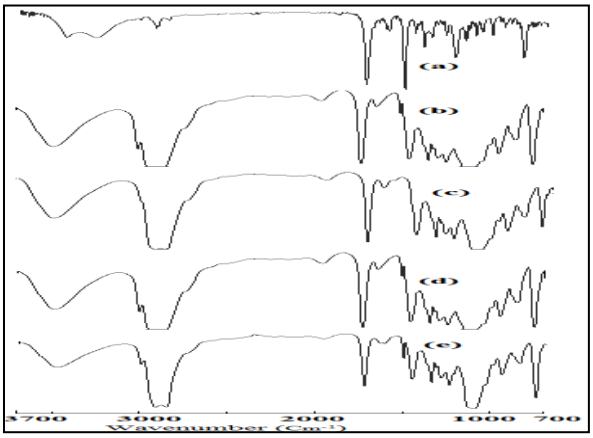

Figure 10(B): FT-IR of (a) Ezetimibe (b) E_4 (c) E_5 (d) E_6 (e) E_7.

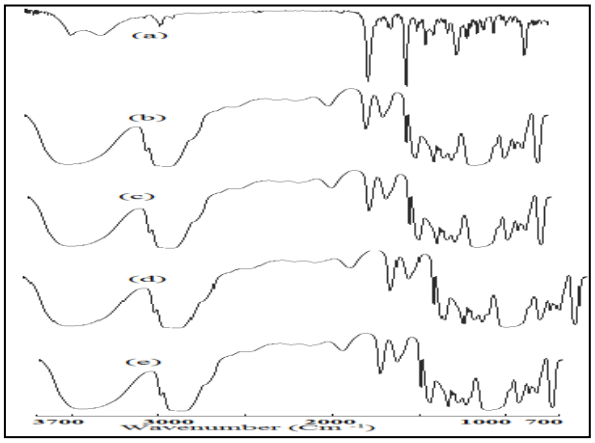

Figure 10(C): FT-IR of (a) Ezetimibe (b) E_8 (c) E_9 (d) E_{10} (e) E_{11}.

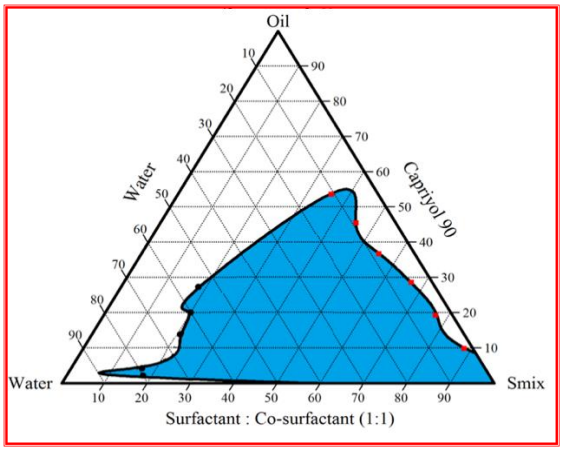

Figure 11: (A) Phase diagram of Capriyol 90, Acrysol K 140/ Capmul MCM C8 & PEG 400 (1:1) and Water.

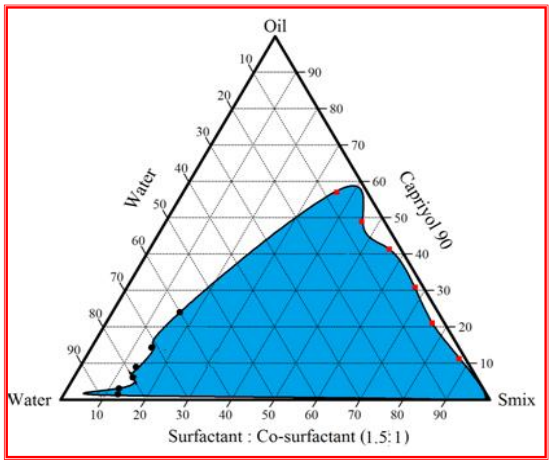

Figure 11: (B) Phase diagram of Capriyol 90, Acrysol K 140/ Capmul MCM C8 & PEG 400 (1:1) and Water.

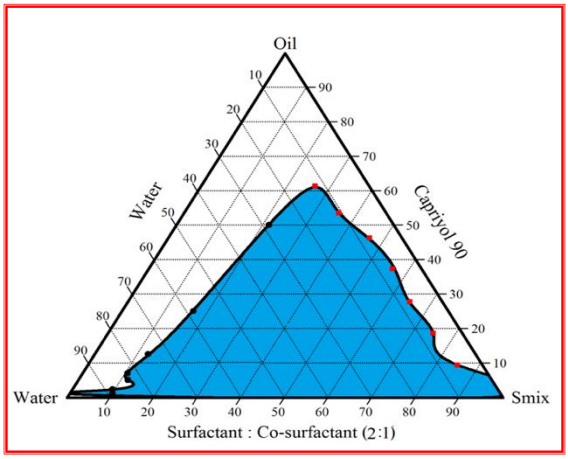

Figure 11: (C) Phase diagram of Capriyol 90, Acrysol K 140/ Capmul MCM C8 & PEG 400 (1:1) and Water.

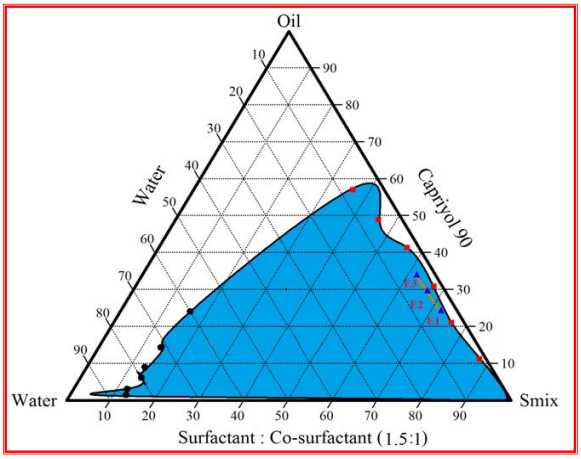

Figure 12: Phase Diagram showing Liquid SMEDDS formulation

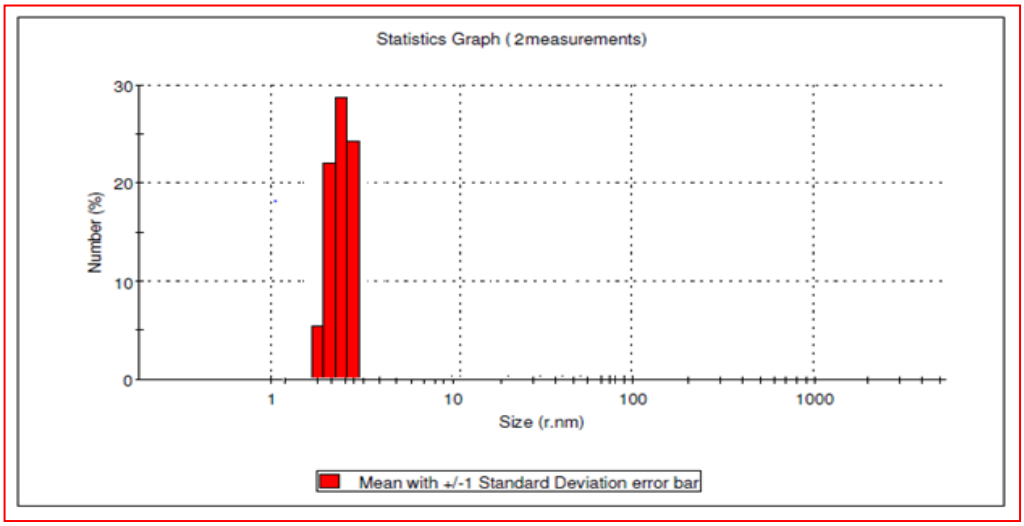

Figure 13: (A) Histograms of particle size distribution of liquid SMEDDS E1

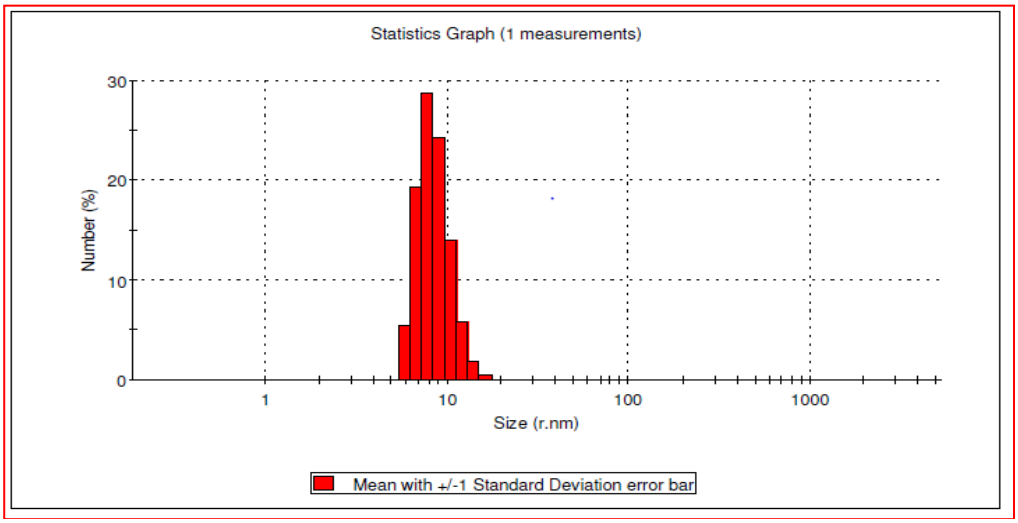

Figure 13: (B) Histograms of globule size distribution of liquid SMEDDS E2

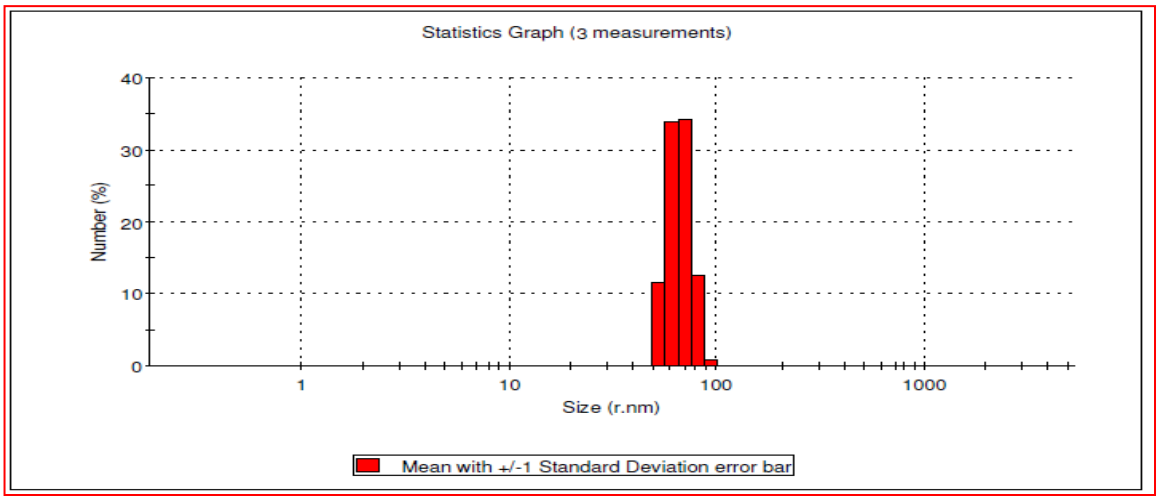

Figure 14: Histograms of particle size distribution of Solid SMEDDS

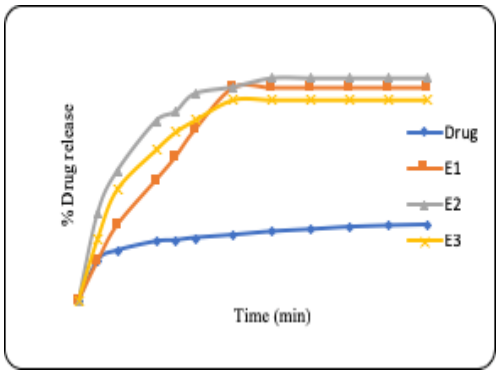

Figure 15(a): *In-Vitro* Dissolution profile of Ezetimibe and various Type I LBF.

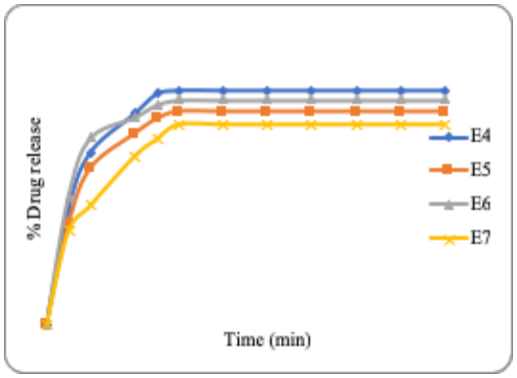

Figure 15(b): *In-Vitro* Dissolution profile of various Type IV LBF containing only surfactant.

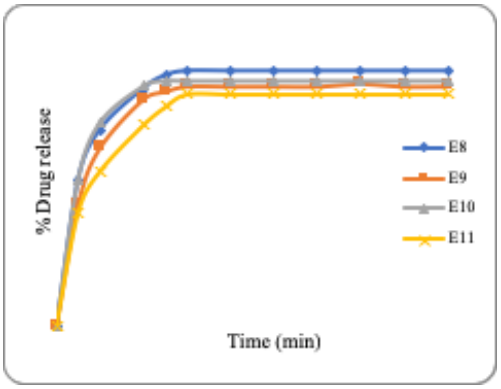

Figure 15(c): *In-Vitro* Dissolution profile of various Type IV LBF containing surfactant and co-surfactant

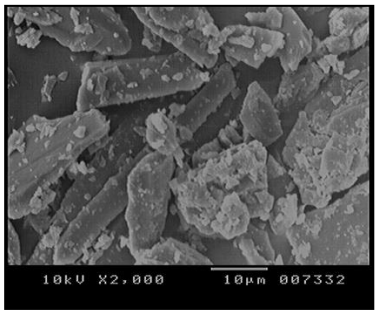

Figure: (A)

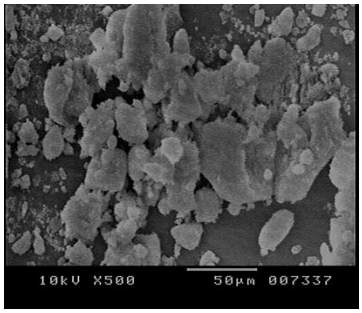

Figure: (B)

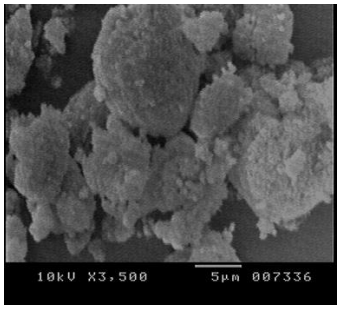

Figure: (C)

Figure 16: Scanning Electron Micrograph of (A) Ezetimibe, (B) Aerosil 200, (C) Solid-SMEDDS

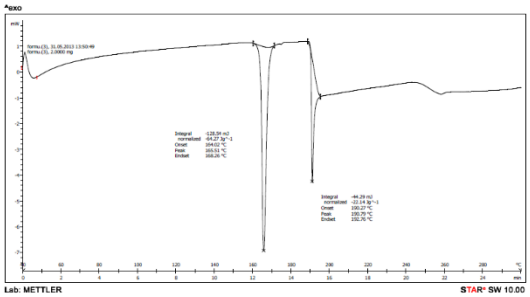

Figure 17: (A) Differential Scanning Calorimetry spectra of Ezetimibe

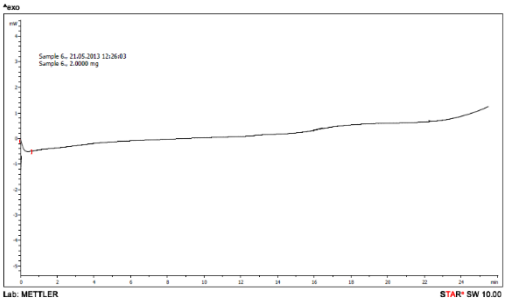

Figure 17: (B) Differential Scanning Calorimetry spectra of Solid SMEDDS

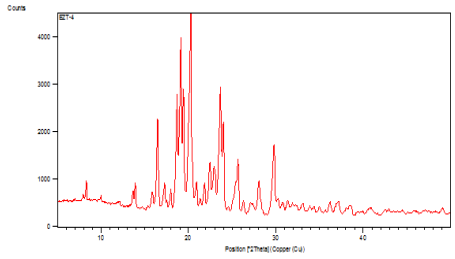

Figure :(A)

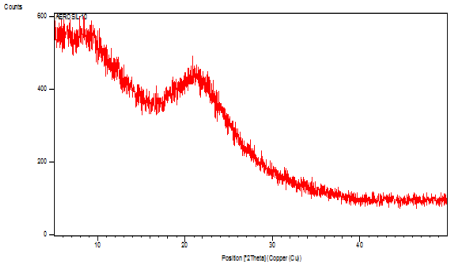

Figure: (B)

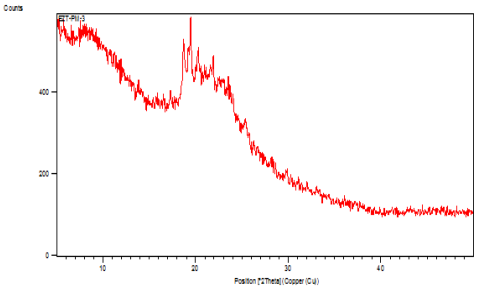

Figure: (C)

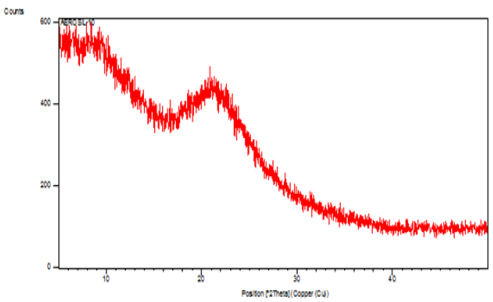

Figure: (D)

Figure 18: X-ray Powder Diffraction Spectra of (A) Ezetimibe, (B) Aerosil 200 (C) physical mixture of Ezetimibe and Aerosil 200, (D) SNGs

CONCLUSION

An optimized SMEDDS formulation consisting of Capriyol 90 (Oil), Capmul MCM C8 & PEG 400 in 1:1 ratio as Co-surfactant and Acrysol K 140 as Surfactant was successfully developed with an increased dissolution rate, increased solubility, and, ultimately, increased bioavailability of a poorly water-soluble drug, Ezetimibe. The developed formulation showed higher pharmacodynamic potential as compared with plain Ezetimibe. Liquid SMEDDS is converted in to Solid-SMEDDS by spray drying technique using Aerosil 200 as a solid carrier and characterized for solid state using DSC, SEM and XRD diffraction. Solid state characterization of S-SMEDDS shows that Ezetimibe is present in the molecularly dissolved state in the S-SMEDDS. In-Vitro dissolution study of Ezetimibe, Liquid and Solid SMEDDS shows that dissolution rate of Ezetimibe dramatically increases by formulating Self Micro-Emulsifying formulation.

Results from stability studies confirmed the stability of the developed formulation. Thus, our study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Ezetimibe to improve its bioavailability.

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