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Original Article

OPTIMIZATION OF COCONUT OIL BASED SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEMS OF OLMESARTAN MEDOXOMIL BY SIMPLEX CENTROID DESIGN

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ABSTRACT

Objective: To develop and optimize self-micro emulsifying drug delivery systems of Olmesartan Medoxomil using formulation by design approach for improvement of solubility and dissolution rate.

Methods: A simplex centroid design was employed as statistical tools to optimize the formulation variables, X_1 (Coconut oil), X_2 (Kolliphor RH) and X_3 (PEG 400). The high and low levels of these factors were selected according the micro-emulsion region obtained from the pseudo-ternary phase diagram. The response variables studied were mean globule size (Y_1) and average absorbance (Y_2).

Results: The optimized formulation consisted of 21.54% of coconut oil, 36.04% of Kolliphor RH and 42.42% of PEG 400 which could provide a globule size of 125.94 nm and an average absorbance of 0.85. Dissolution studies revealed a marked increase in dissolution of the optimized formulation when compared with the pure drug.

Conclusion: Thus, it was concluded that self-micro emulsifying drug delivery systems (SMEDDS) provided a promising formulation approach for the solubility and dissolution enhancement of the poorly soluble drug, Olmesartan Medoxomil.

Keywords: Olmesartan, SMEDDS, Simplex-centroid, Coconut oil

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INTRODUCTION

Olmesartan medoxomil (OLM), is a selective and competitive angiotensin-II receptor blocker that has been approved to treat hypertension. Chemically OLM is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(2-hydroxypropan-2-yl)-2-propyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl] imidazole-4-carboxylate (fig. 1) [1]. It is a prodrug that is rapidly hydrolyzed to form olmesartan by esterases found in plasma, gastrointestinal tract, and liver during absorption. Olmesartan, the active metabolite causes dose-dependent reduction of blood pressure, vasodilation and sodium retention. A clinical trial conducted among hypertensive patients have revealed that OLM displayed excellent pharmacological action with no major adverse effects and a good tolerance. OLM also demonstrated positive effects when used in liver disorders, atherosclerosis, and diabetic nephropathy [2].

However, OLM is hampered by its poor water solubility with an oral bioavailability of merely 26% in healthy humans [3]. This is due to its high lipophilicity with a LogP value of 5.55. Its poor bioavailability is also caused by the unfavorable breakage of OLM in GI fluids to olmesartan. Olmesartan, the parent molecule, has poor permeability with a LogP of 1.2 at pH 7. Efflux pumps (P-glycoprotein) that are found in the GI tract also hamper the absorption of OLM [4].

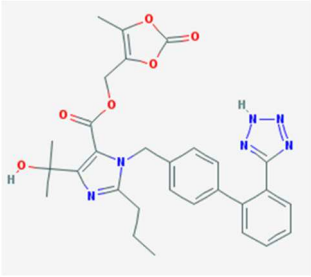

Fig. 1: Chemical structure of olmesartan medoxomil

Self-micro emulsifying drug delivery system (SMEDDS) is one of the methods employed to increase the solubility and dissolution rate of poorly water-soluble drugs. It consists of an isotropic mixture of oils, surfactants, and co-surfactants that when used in combination and at optimal concentrations, promote self-emulsification of the drug. When diluted in an aqueous phase and upon mild agitation, fine, translucent, oil-in-water (o/w) micro-or nanoemulsions are formed. In the body, the GI fluid act as the aqueous phase whereas mild agitation is provided for by the motility of the GI tract.

SMEDDS are stable preparations, unlike regular emulsions, and have an increased interfacial surface area. These increased surface areas allow a sizeable enhancement in the rate and extent of oral absorption [5-8]. An enhanced fluidization of the intestinal membrane and subsequently, transcellular absorption facilitation contributes to drug absorption. Furthermore, paracellular transport is facilitated by the opening of tight junctions. Drug absorption is also enhanced by efflux pumps inhibition such as P-gp.

The interfacial surface area of SMEDDS is inverse to its globule diameter. A drug formulated as SMEDDS is thus dispersed as fine droplets in the gastrointestinal (GI) tract. Such characteristic helps to improve its dissolution profile and subsequently, its absorption and bioavailability. Examples of drugs that have been made commercially available as self-emulsifying systems include Cyclosporine A, Ritonavir, and Saquinavir. They are marketed as Neoral ®, Norvir ®, and Fortovase ® respectively [9, 10].

The crucial step in the formulation of SMEDDS, is in determining the appropriate oil, surfactant, and co-surfactant that can thoroughly dissolve the drug at its therapeutic concentration range. The literature lacks any data about the optimization of SMEDDS for the improvement in OLM solubility and dissolution. Thus, the aim of this study was to design and optimization of OLM-loaded SMEDDS. A simplex centroid design was applied, and desirability function was used to optimize the concentration of oil, surfactant, and cosurfactant. As part of the optimization process, the main effect and the interaction effects of amounts of oil, surfactant and co-surfactant on globule size and absorbance were investigated. The optimized formulation exhibiting minimum globule size and maximum

absorbance which will result in increased solubility and vitro drug dissolution is anticipated to improve oral absorption of the drug.

In this study, we propose to develop OLM SMEDDS using natural oils as they are abundantly available, less expensive and biocompatible. The formulation components studied and optimized for this study were coconut oil, Kolliphor RH and PEG 400 as oil, surfactant, and cosurfactant respectively.

MATERIALS AND METHODS

Materials

Olmesartan medoxomil was purchased from Nivon Specialties (Mumbai, India). Kolliphor® RH 40 (Macrogolglycerol hydroxy stearate) was obtained from BASF (Ludwigshafen, Germany). PEG 400 (Poly (ethylene glycol)) was obtained from Sigma-Aldrich (Missouri, USA Coconut oil was obtained from ChemSoln (Selangor, Malaysia). Acetonitrile and potassium dihydrogen phosphate were purchased from Merck, Darmstadt, Germany. All other chemicals were of analytical grade and were used as received.

Methods

Solubility studies

Solubility studies were conducted by adding an excess of OLM (around 50 mg) in 1 ml of the vehicle to determine the solubility of OLM in various oils, surfactants and co-surfactants. The mixtures were vortexed using a vortex mixer (LMS, Mixer Uzusio, VTX-3000L) and kept in a water bath shaker (Julabo, TW20) at 50 °C for 48 h to allow the mixtures to equilibrate. After 48 h, the supernatant was removed using a pipette and centrifuged (Hettich, Mikro 22 R) for 10 min at 4000 rpm to sediment all the excess insoluble OLM. A 0.1 ml of the centrifuged supernatant was drawn up using a micropipette and was made up to 10 ml with methanol. 1 ml of the diluted sample was subsequently made up to 10 ml with methanol for a total dilution factor of 1000. The samples were then quantified using the HPLC method detailed below.

HPLC method

The quantitative estimation of OLM in the SMEDDS formulations and dissolution fluids was performed by HPLC. The HPLC system (Perkin Elmer, Flexar LC System) employed was equipped with a pump (Flexar FX-10), a diode array detector (Flexar PDA Plus), an autosampler (FX UHPLC Autosampler) and a data system (Chromera Chromatography Data System). Samples were separated by using a Brownlee Analytical Perkin Elmer C18 column. A modified HPLC method reported by Kumanan *et al.* is used in this study [11]. The mobile phase used was a mixture of Acetonitrile-0.05M Potassium dihydrogen phosphate adjusted to pH 3.0 with orthophosphoric acid at a ratio of 50:50, v/v. The filtered (filtered through 0.45 µm membrane filter) mobile phase components were pumped at a flow rate of 1.0 ml/min. The column temperature of the system was maintained at 30 °C. The eluents were monitored at 256 nm.

Ternary phase diagram

Ternary phase diagrams are essential in defining the number and different types of phases formed. The addition of OLM may interfere to a certain degree with the process of self-emulsification causing an alteration in the optimal oil-surfactant ratio [12, 13]. Hence, ternary phase diagrams are constructed to determine the optimal concentration of oil, surfactants and co-surfactant [14].

The oil studied was coconut oil whereas Kolliphor RH 40, was investigated as a surfactant. PEG 400 was explored for its use as a co-surfactant. For all mixtures, the amount was always added to a total of 100%. The components in the mixtures were thoroughly mixed using a vortex mixer and the efficiency of self-emulsion formation of each formulation was assessed by adding 0.1 ml of each mixture to 20 ml of double distilled water in a conical flask.

The SMEDDS formed were assessed visually on its final appearance. Ternary plot diagrams were constructed using ProSim free software in order to determine the self-emulsification region. Only emulsions that were clear or tinged slightly bluish were accepted as SMEDDS.

Preparation and optimization of OLM-SMEDDS formulations

20 mg of OLM was accurately weighed and added to the formulation. The mixture was then heated in a water bath at 50 °C for 24 h to ensure complete solubilization. Based on the ternary phase diagram, the oil, surfactant, and cosurfactant chosen were coconut oil, Kolliphor RH 40, and PEG 400 respectively [15].

A Simple Centroid experimental design was used to develop and optimize the OLM formulations procedure using Design Expert software (9.0.6). The independent factors and response variables that were observed in this design are shown in table 1. The effects of independent factors on response variables (Y_1: mean globule size of diluted SMEDDS, Y_2: average absorbance) were investigated. A total of 11 experiments were designed by the software and the order of experiments was run in random to increase predictability of the model.

Optimization was performed using a desirability function to obtain the levels of X_1, X_2 and X_3, which minimized (Y_1) and maximized (Y_2) [16, 17].

Table 1: Formulations of simplex centroid design along with the response variable values. Actual values of globule size and absorbance of eleven different batches

Batch	Coconut oil	Kolliphor RH	PEG 400	Mean globule size (nm)	Average absorbance of the diluted SEDDS	Emulsification time (s)
1	30%(1)	30%(0)	40%(0)	642.1±15.9	0.27±0.03	45
2	10%(0)	50%(1)	40%(0)	46.91±4.56	1.15±0.08	13
3	10%(0)	30%(0)	60%(1)	49.4±5.57	1.35±0.08	11
4	20%(0.5)	40%(0.5)	40%(0)	64.49±4.63	0.97±0.06	15
5	20%(0.5)	30%(0)	50%(0.5)	42.74±4.05	0.83±0.02	18
6	10%(0)	40%(0.5)	50%(0.5)	51.13±3.73	1.25±0.04	14
7	16.67%(0.33)	36.67%(0.33)	46.67%(0.33)	71.66±4.89	1.14±0.03	15
8	23.33%(0.67)	33.33%(0.17)	43.33%(0.17)	97.12±1.71	0.65±0.04	17
9	13.33%(0.17)	43.33%(0.67)	43.33%(0.17)	86.17±3.3	1.08±0.04	16
10	13.33%(0.17)	33.33%(0.17)	53.33%(0.67)	28.47±3.4	1.19±0.05	14
11	30%(1)	30%(0)	40%(0)	687.5±26.5	0.24±0.03	48

Characterization of OLM-Loaded SNEDDS

Emulsification time

Emulsification time is an important assessment and acceptable SMEDDS/SNEDDS should rapidly emulsify. A Grade 1 emulsion should be formed within 1 minute and Grade 3 emulsion within 3 min of dilution and agitation [18]. In order to assess the emulsification time (the time required for a formulation upon dilution to form a homogenous, emulsified mixture), 0.1 ml of formulation was added to 20 ml of double distilled water at 37 °C. A magnetic stirrer was used to provide gentle agitation. The optimized formulations were visually assessed according to the rate of emulsification.

Droplet sizes analysis

The droplet size affects the rate and extent of drug release as well as the stability of the emulsion. Several common techniques used to determine the emulsion droplet size distributions include Photon Correlation Spectroscopy (PCS), Laser Diffraction and Coulter Counter [19]. Not only

does droplet size influence the rate and extent of drug release, but it also affects the oral absorption of the drug. Hence, it is preferable that the droplet size should be as fine as possible.

The droplet size of the 11 formulations was analyzed using a Malvern Zetasizer, Nano-ZS. A 0.1 ml of formulation was introduced to 20 ml of purified water at 25 °C and the contents gently stirred with a magnetic stirrer. The resultant droplet size was determined by photon correlation spectroscopy. A laser beam at 632 nm wavelength was used, and light scattering was monitored at 25 °C at a 173 ° angle.

Dissolution studies

Dissolution studies were performed for the optimized formulation and the pure drug. An amount corresponding to 10 mg was filled into size 0 hard gelatine capsules and held to the bottom of the vessel using copper sinkers. The in vitro dissolution behaviors of the optimized SMEDDS formulation and the pure drug were assessed using the USP rotating paddle Electrolab Dissolution Tester (TDT-08L).

The dissolution media (0.1 N HCl) was kept at 37±0.5 °C and a rotation speed of 50 rpm was maintained. Once optimal conditions were achieved, the optimized OLM-loaded SMEDDS and the pure drug (10 mg) were placed into the media. 5 ml aliquots were withdrawn at predetermined time intervals (10, 20, 30, 45, and 60 min). The withdrawn samples were replaced with an equal amount of fresh dissolution media to maintain sink conditions. The samples collected were filtered using a 0.45 mm Millipore nylon filter and analyzed using HPLC at λ = 256 nm. The release profiles from OLM-loaded SMEDDS (10 mg) were compared to the release profile of pure drug of OLM [20, 21].

Transmission electron microscopy

OLM-loaded SNEDDS were evaluated using transmission electron microscopy (FEI TECHNAI G2 20S TWIN) to examine their morphology and structure. A Zeiss 902 CEM microscope (Zeiss, Barcelona, Spain) was used. The sample was diluted with distilled water (1:200) and thoroughly mixed by gentle shaking [22]. One sample droplet was deposited on a copper grid and the excess was absorbed using a filter paper. Subsequently, the grid was inverted and stained with one drop of 1% phosphotungstic acid (PTA) for 10s. Excess PTA was removed and examination of the grid was done at 60–80 kV.

RESULTS

Solubility studies

SMEDDS consists of a mixture of oil, surfactants, co-surfactants, and drug. When introduced to an aqueous phase, the mixture should form a clear, monophasic liquid at room temperature and should have good solvent properties that allow the drug to be present in solubilized form. The solubility of OLM in various vehicles is shown in table 2. Amongst the various oily phases screened, Coconut oil has shown the maximum solubility and hence coconut oil is chosen as the oily phase for this study. Among the two surfactants studied, namely Kolliphor RH and Tween® 80, Kolliphor RH had shown maximum solubility and hence Kolliphor RH is chosen as the surfactant in this study. PEG 400 was used as a co-surfactant as it had exhibited better solubility for OLM compared to Glycerol.

Table 2: Solubility studies of OLM in different vehicles

Type of vehicle	Solubility (mg/ml)±SD, n=3
Castor Oil	1.39±0.18
Corn Oil	0.87±0.18
Coconut oil	1.59±0.22
Palm Oil	1.09±0.16
Sesame Oil	0.68±0.17
Sunflower Oil	1.25±0.13
Olive Oil	0.98±0.14
Tween 80	16.19±3.17
Kolliphor RH	18.49±2.74
PEG 400	23.42±2.25
Glycerol	18.89±0.55

Ternary phase diagram

Phase diagrams are used to develop SMEDDS which can form thermodynamically stable, isotropic, clear oil in water dispersions. They are usually constructed to identify the self-emulsifying region and to select a suitable concentration of oil, surfactant, and cosurfactant for form the SEDDS. The ternary phase diagram for the system containing coconut oil, Kolliphor RH and PEG 400 is shown in fig. 2. The cordoned areas shaded yellow represents the region of efficient self-emulsification for the respective series.

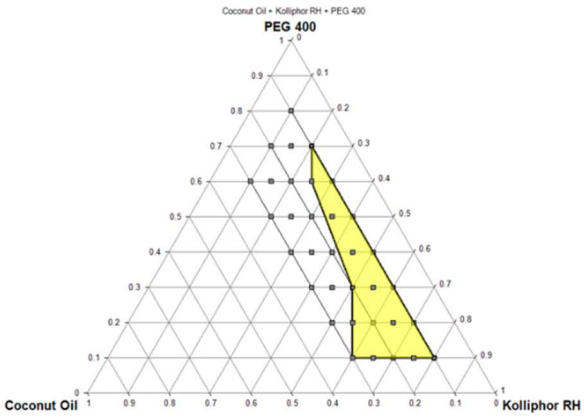

Fig. 2: Ternary phase diagram for combination of Coconut oil, Kolliphor RH, and PEG 400

Emulsification time

The self-emulsifying efficiency of a formulation can be primarily projected by determining the rate of emulsification. The SNEDDS should be quickly and completely dispersed when subjected to aqueous dilution and mild agitation [23]. The time emulsification investigation showed that the formulations (batch 2-10) emulsified within 20 seconds whereas batches 1 and 11 took around 50 seconds. As all the batches emulsified in less than 1 minute, it can be concluded that all the batches can be classified and grade 1 emulsions suggesting a rapid rate of the emulsification [18]. It is apparent that rapid emulsification corresponds to a lower oil content and higher co-surfactant content, resulting in a system with lower viscosity.

Globule sizes analysis

The globule size in considered to be an important factor in self-emulsification performance because it determines the rate and extent of drug release and absorption [24]. Results show that the prepared SMEDDS have a globule size of less than 100 nm except batches 1 and 11 which has shown larger globule sizes of more than 600 nm.

Optimization of OLM formulation

Based on ternary phase diagram (fig. 2), the ranges of coconut oil (Factor A), Kolliphor RH (Factor B), and PEG 400 (Factor C) were varied from 10 to 30% (w/w), 30 to 40% (w/w), and 50 to 60% (w/w) respectively. A simple centroid experimental design containing 11 runs generated by Design Expert ® software was used to optimize the components of OLM-SMEDDS. Mean globule size and average absorbance were selected as response variables. The high values of correlation coefficients for mean globule size (R^2 = 0.9627) and average absorbance (R^2 = 0.9873) indicate a good fit which indicates a good agreement between the independent and response variables. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries either positive or negative. A positive sign of the coefficient indicates a synergistic effect while a negative sign indicates an antagonistic effect on the response. The larger coefficient means the independent variable has a more potent influence on the response.

Mean globule size

All the batches have shown a globule size for less than 100 nm ranging from 29.6 nm to 97.33 nm except batches 1 and 11 which had shown very high globule size greater than 600 nm. Regression analysis for response Y_1 (mean globule size) suggested a quadratic model and the cubic model was aliased due to insufficient design points. ANOVA data suggested the model to be significant ($p = 0.0014$). The polynomial equation for mean globule size proposed by the model is as follows:

$$Y_1 = +21813.8[X_1] - 798.4[X_2] - 89.9[X_3] - 27725.1[X_1X_2] - 30723.8[X_1X_3] + 4661.2[X_2X_3]$$

Synergistic effects of X_1 and X_2X_3 and antagonistic effects of X_2, X_3, X_1X_2, and X_1X_3 on Y_1 were observed. Mean globule size was lowest in Batch 10 at low levels of oil (13.33%), low-level of surfactant (33.33%) and high level of co-surfactant (53.33%). Table 1 shows that with an increase in the proportion of oil, the globule size was decreased and the absorbance of the diluted SMEDDS was increased indicating a higher solubility.

Average absorbance

The absorbance of all the batches ranged from 0.24 to 1.35. Regression analysis for response Y_2 (average absorbance) suggested a quadratic model and the cubic model was aliased due to insufficient design points. ANOVA data suggested the model to be significant ($p<0.0001$). The polynomial equation for mean globule size proposed by the model is as follows:

$$Y_2 = -11.39[X_1] - 1.06[X_2] + 2.59[X_3] + 26.6[X_1X_2] + 3.05[X_1X_3] + 1.55\ [X_2X_3]$$

Synergistic effects of X_3 and X_1X_2, X_2X_3 and X_1X_3 and antagonistic effects of X_1 and X_2, on Y1 were observed. The average absorbance of was found to be highest for batch 3 at low levels of oil (10%), low-level of surfactant (30%) and high level of co-surfactant (60%) indicating a high solubilization of the drug which will result in improved dissolution.

Response surface and contour plot analysis

The relationship between the independent and response variables was further elucidated using contour and response surface plots. These types of plots are very useful for studying the interaction effects between the two factors for understanding how the effect of one factor will be influenced by the change in the level of another factor as shown in fig. 3 (A and B). As these types of plots can only express two independent variables at a time against the response, one independent variable must always be fixed [25].

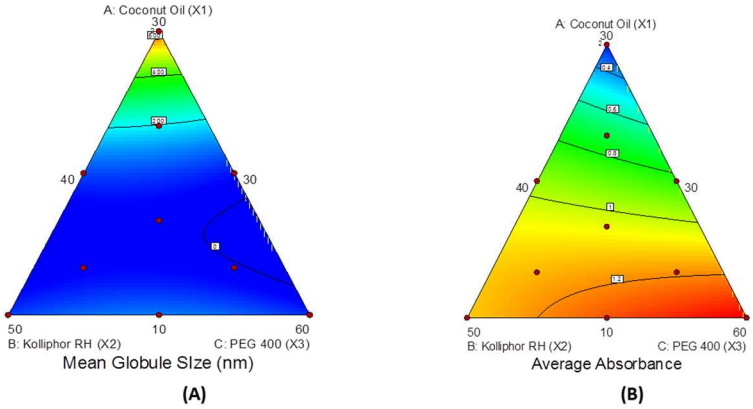

Fig. 3: Contour plots for (A) mean globule size; (B) average absorbance

Identification and evaluation of optimum formulation using the desirability function

For the analysis of experiments with multiple responses, desirability function technique is used where several responses have to be optimized simultaneously. In this case, Y_1 was set to be minimized whereas Y_2 was set to be maximized. The desirability function D, over the experimental domain, was calculated by DesignExpert (9.0.6) software. The scale of desirability function ranges between D=0, for a completely undesirable response and D=1, if the response is at the most desirable value. OLM SMEDDS formulation with a composition of 21.54% of Coconut oil, 36.04% of Kolliphor RH and 42.42% of PEG400 was observed to be optimal, in terms of desired globule size (minimum) and average absorbance (minimum). Fig. 4(A) shows the highest desirability (0.668) and fig. 4(B) shows the overlay plots with optimum globule size (125.94 nm) and average absorption (0.85).

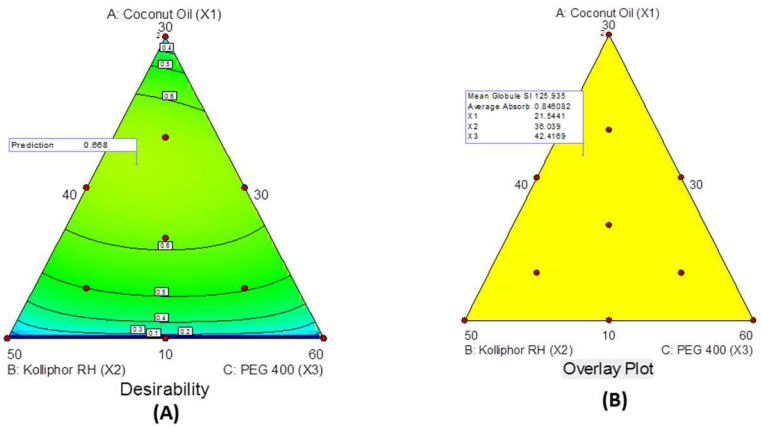

Fig. 4: (A) Contour plot of the results with desirability value; (B) Overlay plot for the optimization of Coconut oil, Kolliphor RH and PEG 400

Dissolution studies

In vitro dissolution studies were carried out in 0.1N HCl. The dissolution performance of the optimized SMEDDS was compared with that of the OLM pure drug. The release profiles are shown in fig. 5 (n = 3). The percentage drug release for the optimized OLM SMEDDS was found to be 98.3% in 20 min whereas it was only 32.3% for the OLM pure drug in 60 min. The faster dissolution from the SMEDDS formulation can be attributed to the fact that, the drug is insolubilized form in the formulation and upon exposure to the dissolution medium it results in the formation of smaller droplets that can dissolve rapidly in the dissolution medium.

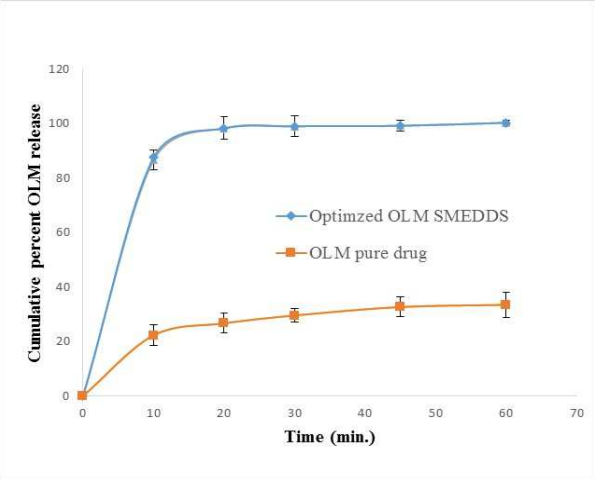

Fig. 5: *In-vitro* release profile of optimized OLM SMEDDS and OLM pure drug (n = 3).

Transmission electron microscopy

Morphological and structural examination of the optimized OLM-loaded SNEDDS formulation was carried out using transmission electron microscopy. TEM images post-dilution showed that spherical micelles were formed with sizes less than 100 nm (fig. 6). These results were according to zeta sizer results with no signs of coalescence confirming the efficiency of the nanoemulsion preparation method used. The nanoemulsion droplets emerged as dark and the surroundings were found to be bright. No signs of drug precipitation were observed inferring the stability of the formed nanoemulsion. Closer analysis of TEM images reveals that each globule is surrounded by a thick layer indicating the formation of monolayer around the emulsion droplets, reducing the interfacial energy, and forming a barrier to coalescence [22].

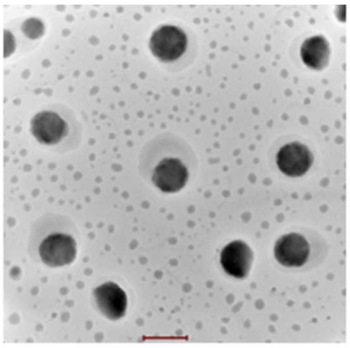

Fig. 6: TEM of optimized olmesartan SNEDDS formulation (Bar length 50 nm)

CONCLUSION

The design and optimization of OLM SMEDDS formulation were carried out by Simplex-Centroid design combined with desirability function. The effect of the amount of oil, surfactant and co-surfactant were investigated for their influence on globule size and absorbance of dilute SEDDS. The optimized formulation consisted of 21.54% of coconut oil, 36.04% mg of Kolliophor RH and 42.42% of PEG 400 which could provide a globule size of 125.94 nm and an average absorbance of 0.85. Dissolution of optimized SMEDDS formulation was significantly higher than the pure drug. Thus, the present study illustrates the potential use of SMEDDS formulation approach for the improvement of solubility and dissolution rate of the poorly soluble drug, Olmesartan Medoxomil.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests

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