



Original Research Paper

Unlocking the Delivery Potential of Lutein: Development and Optimization of a Liquid Self-Emulsifying Drug Delivery System

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ABSTRACT

The present study aimed to design, optimize, and systematically evaluate a liquid self-emulsifying drug delivery system (L-SEDDS) of lutein to accelerate solubility and dissolution rate. L-SEDDS formulations were formulated using medium-chain triglyceride oil (oil phase), Tween 80 (surfactant), and Span 20 (co-surfactant) based on solubility studies to optimize the formulation; the effects of oil and Smix concentrations on drug release and emulsification time were assessed using a 3² factorial design. The optimized formulation showed a desirability of 0.912, and the optimization research showed that increasing Smix concentration and decreasing oil content greatly improved drug release and decreased emulsification time. The optimized (F5) L-SEDDS contains 20% oil and 80% Smix it consisted of a viscosity of 132 mPas, drug content of 98.67%, and emulsification time of 34 seconds. Dissolution in pH 6.8 phosphate buffer demonstrated a cumulative drug release of 98.89% within 30 minutes. The mean droplet size was 462.8nm with a PDI of 0.379, and -39.4mV zeta potential showed good stability of the formulation. The formulation remained stable at accelerated storage conditions with no significant change in emulsification time or dissolution behavior.

Keywords: Lutein; L-SEDDS; self-emulsifying drug delivery system; S-SEDDS; Solubility; dissolution; zeta potential

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INTRODUCTION

Oral drug delivery is the general route of drug administration. It is economical, comfortable, convenient, and requires no special training for use. However, 40- 70% have been estimated to be very slightly water-soluble or lipophilic compounds to permit consistent oral absorption to assure therapeutic efficacy. They have solubility and drug release-related bioavailability issues. The absorption of lipophilic material is usually dissolution rate limited¹⁻³.

Generally, absorption of a drug mainly depends on two factors: one is solubility, and another is permeability⁴⁻⁶. Lutein also belongs to the BCS class II drug, which has low solubility and high permeability, a member of the xanthophyll carotenoid family^{7,8}. Lutein act as an antioxidant and also protect the plants from the damage of photo-induced free radicals and improves eye health⁹⁻¹¹.

Increased dietary intake of lutein has been associated with a minimized risk of age-related macular degeneration (AMD), which is one of the main causes of blindness in aged populations¹²⁻¹⁴. It also shows anticancer, cardiovascular, neuroprotective, skin protective and anti-aging activities^{15,16}. It gives chemoprotection against atherosclerosis, lowers serum and hepatic cholesterol, and has angioprotective activity in diabetic retinopathy^{17,18}.

The present work aims to design, characterize and evaluate a lutein SEDDS to accelerate the dissolution and solubility of drug by systematic optimization of the oil, surfactant and co-surfactant ratios based on a pseudo-ternary phase diagram.

MATERIAL AND METHODS

Material

Lutein (78%), Sunflower Lecithin, mixed tocopherol MCT oil, Tween 80, and Span 20 were gifted by the well-known pharmaceutical industries.

Solubility Study

The solubility of lutein was studied in various vehicles such as oil, Surfactant, co-surfactant, ethanol, and pH 6.8 phosphate buffer. An excessive amount of lutein was put in 10 mL of each vehicle and stirred for 24 hrs on a magnetic stirrer. After 24 hrs completion the mixture was filtered out with the help of Whatman filter paper. Then, 1 mL from that filtered solution check the absorbance on a UV spectrophotometer at 446 nm¹⁹⁻²¹.

Creation of Pseudo-ternary phase diagram

A pseudo-ternary phase diagram was created by the aqueous titration method at room temperature in the absence of lutein to determine the self-emulsifying zone. On the basis of the solubility study, MCT oil, Tween 80, and Span 20 were chosen as oil phase, surfactant, and co-surfactant for preparation of lutein-loaded L-SEDDS. Tween 80 and Span 20 were mixed at different ratios (Smix ratio), viz. 1:1,

2:1, 3:1. For each pseudo ternary phase diagram, Oil and Smix were added thoroughly at various ratios ranging from 1:9 to 9:1. Each mixture was titrated dropwise with purified water at room temperature under gentle stirring with help of a magnetic stirrer. When it reached its equilibrium state, the liquid or emulsion form was visually determined by the blue and milky white appearance or its transparency. Visual observation of the spontaneous emulsification tendency and progress of emulsion droplets was also performed. The tendency of emulsion formation was graded as “good” if the droplets were dispersed rapidly in distilled water to give a fine, homogeneous, milky emulsion and “bad” if there were no emulsion formation and rapid coalescence of the oil, mainly after stopping the stirring. The titration continued until the appearance of turbidity or phase separation. Good self-emulsifying regions were determined and the phase diagram was constructed. Formulations that resulted in clear, transparent, homogeneous, bluish or slightly milky emulsion without phase separation within the region of self-emulsification were investigated and selected for further development of lutein-loaded L-SEDDS^{22,23}.

Experimental Method

In this method, 2 factors were analyzed at three levels each, and Design-Expert software was used to conduct experimental trials using all nine conceivable combinations. The concentration of oil phase (MCT oil) (A) and Smix concentration (Tween 80: Span 20 mixture) (B) were chosen as independent variables in this investigation. The dependent variables were chosen to be the emulsification time and in vitro performance traits^{24,25}.

The nine formulations were developed with different amounts of oil and Smix concentrations. Y1 (emulsification time) and Y2 (in vitro performance attributes) were the dependent variables^{26,27}.

Table 1. List of Independent and Dependent Variables in 3² Factorial Design

A. Independent factors	A	Concentration of oil (%)
	B	Concentration of Smix (%)
B. Dependent factors	Y1	% Drug releases
	Y2	Emulsification time

Table 2. Variables in 3² Factorial Designs

Independent Variables	Levels		
	-1	0	+1
Oil(A)	10 %	20 %	30 %
Smix(B)	70%	80 %	90 %

Table 3. Factorial Design of SEDDS Batches

Batch No.	A	B	Actual Value (%)	
F1	-1	-1	10	70
F2	0	+1	20	90
F3	+1	-1	30	70
F4	-1	+1	10	90
F5	0	0	20	80
F6	+1	+1	30	90
F7	-1	0	10	80
F8	0	-1	20	70
F9	+1	0	30	80

Preparation of L-SEDDS and S-SEDDS

Lutein-loaded self-emulsifying drug delivery system (L-SEDDS) was prepared by the spontaneous emulsification technique using magnetic stirring. Mixed tocopherol was first mixed with the required amount of MCT oil with continuous stirring. The mix of Tween 80 and Span 20 was then slowly added into the oil phase to form a clear homogeneous mixture. Lutein was transferred to the system with uniform stirring till it was completely dissolved, and sunflower lecithin was added. The formulation was continuously stirred till the formation of a clear isotropic mixture. The formulation was further stored for evaluation studies^{28,29}.

Evaluations:**Viscosity**

The viscosity of lutein-loaded L-SEDDS formulations was determined using HAAKE Viscotester 3 (Model R) at a temperature of 25 ± 1 . The L-SEDDS formulation was transferred into the sample vessel, which was filled up to the mark present on spindle no. R3L, and viscosity was determined. The instrument was run for 3 min to provide a stable reading. The viscosity values were recorded in mPas unit^{30,31}.

Emulsification Time

The emulsification time of lutein-loaded L-SEDDS formulations was checked by USP dissolution paddle apparatus II (Electrolab TDL 06L). 1ml of L-SEDDS preparation was transferred to 500ml distilled water, which was stirred at 50rpm with the help of a stainless steel paddle³².

Determination of Drug Content

The measured quantity (1ml) of lutein-loaded L-SEDDS equivalent to 20 mg of lutein was pour in 10ml volumetric flask, and the volume make up with ethanol. The solution was sonicated till the clear solution was obtained. From this solution 1ml was taken and diluted further upto 10ml with ethanol. The resulting solution was filtered through membrane filters to remove any undissolved particles. The absorbance of that filtered solution was determined at 446 nm using a UV-visible spectrophotometer. The quantity of lutein was

calculated utilizing the standard calibration curve of ethanol^{33,34}.

In vitro Dissolution Study

It was performed by using the USP II paddle apparatus. 1ml of L-SEDDS formulation, which contains 20 mg of lutein, was added into 900 ml of pH 6.8 phosphate buffer. The rotation speed of the paddle was set as per IP recommendations for immediate release (30 min) at 50 rpm. Samples (5ml) were withdrawn at 5 min intervals and filtered out using a membrane filter. Sink condition maintain by using the same quantity of dissolution medium at each withdrawal. All collected samples were diluted and checked for drug release by UV-visible spectrophotometer at 446 nm³⁵.

In vitro Assessment of Self-emulsification

The favorable entropy change linked to interfacial area expansion causes SEDDS to spontaneously emulsify when they come into contact with an aqueous liquid while being gently stirred. Five grades (A–E) were assigned based on the dilution method's visual assessment of the self-emulsification ability^{36,37}.

Grade A quickly creates a clear/bluish nanoemulsion;

Grade B quickly emulsifies but becomes turbid;

Grade C forms a milky emulsion in two minutes;

Grade D gradually forms a grayish-white, slightly oily emulsion; and

Grade E shows poor emulsification with noticeable big oil globules.

Droplet Size and Zeta Potential Determination

The dynamic light scattering (DLS) technique, based on the Malvern Zetasizer used for the droplet size determination of lutein-loaded L-SEDDS. The formulation was diluted with distilled water for clear dispersion, and the droplet size analysis was performed in a disposable cuvette at 25.

Stability

A stability study was carried out in a stability chamber (6CHM GMP, REMI, Mumbai, India) under controlled environmental accelerated conditions as per ICHQ1A (R2) guidelines³⁸.

Preparation of S-SEDDS from the L-SEDDS Optimized Batch

Aerosil 200 was used as a solid carrier in the adsorption process to create the solid self-emulsifying drug delivery system (S-SEDDS). Aerosil 200 was used to adsorb the optimized L-SEDDS formulation at a concentration of 250 mg per millilitre of L-SEDDS. Using a mortar and pestle, the liquid formulation and carrier were evenly combined until a free-flowing powder was produced. After that, the resulting powder blend was dried for two hours at 40°C in a tray dryer to eliminate any remaining moisture and enhance flow properties³⁹.

Evaluation of S-SEDDS**Micromeritic Properties**

Using conventional techniques, the micromeritic

characteristics of the S-SEDDS powder were assessed in terms of density parameters, angle of repose, Hausner's ratio, and compressibility index. The S-SEDDS powder's flowability, along with packing properties, was evaluated using the acquired parameters.

Emulsification Time and *In-vitro* Dissolution Study:

The same methods outlined for the L-SEDDS were used to assess the S-SEDDS's emulsification time and *in vitro* drug release. A precisely weighed amount of S-SEDDS equivalent to the optimized L-SEDDS formulation was distributed in the aqueous medium for the emulsification investigation, and the amount of time needed for full emulsification was noted. The identical dissolution conditions used for L-SEDDS were applied to the *in vitro* drug release investigation, and the percentage of cumulative drug release was calculated at predefined intervals⁴⁰.

RESULTS AND DISCUSSION

Solubility Study

SEDDS formulation contains oil, surfactant, and co-surfactant. They should have the characteristics to allow the drug to be soluble in it. The solubility of lutein in different solvents is shown in Figure 1. Lutein shows the highest solubility in ethanol (8.75 mg/ml). Followed by MCT oil, Tween 80, Span 20, and pH 6.8 phosphate buffers, which showed 2.372 mg/ml, 1.95 mg/ml, 0.241 mg/ml, and 0.75 mg/ml.

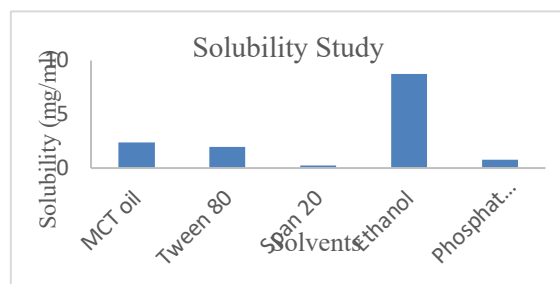


Figure 1. Solubility Study of Lutein with Different Solvents

FTIR and DSC

FTIR of lutein and lutein-excipients mixture confirms the compatibility of lutein with excipients. Lutein showed characteristic peaks corresponding to C=C, O-H, C-H, C-O & =C-H functional groups. In the lutein-excipients mixture, these peaks were maintained with slight shifts, keeping the chemical structure of lutein. 3301.54 or 3474.67 cm^{-1} showed the OH stretching of lutein. The peaks at 2925.92 & 2856.72 cm^{-1} indicated the alkyl chains of MCT oil, Tween 80, and Span 20, and the peak at 1740.61 cm^{-1} corresponded to ester carbonyl groups of the lipidic excipients. The peak at 1246.28- 1099.78 cm^{-1} indicated C-O stretching, confirming the presence of surfactant and co-surfactant (Figure no. 2). The thermal behavior of the lutein was analyzed using differential Scanning

Calorimetry (DSC). The DSC curve of lutein reflected a sharp endothermic peak at 159.1, confirming its crystalline character. The lutein-excipient mixture showed a slightly shifted peak at 156.98, showing partial changes in crystallinity and good physical compatibility with excipients.

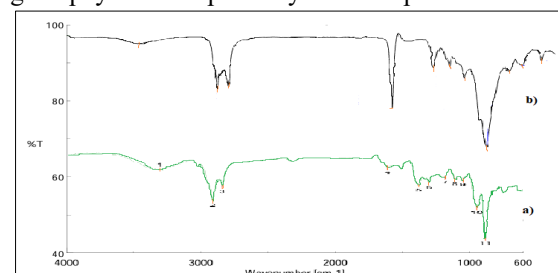


Figure 2. a) FTIR Analysis of Lutein b) FTIR Analysis of Lutein-Excipient Mixture

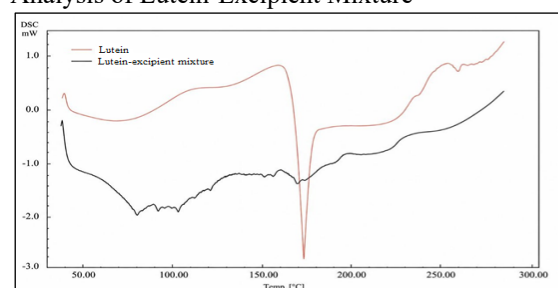


Figure 3. Overlay Plot of Lutein and Lutein-Excipient Mixture

Construction of Pseudo Ternary Phase Diagram

A pseudo-ternary phase diagram was plotted utilizing TernaryPlot.com software by the aqueous titration method. The diagram determines the self-emulsification zone of SEDDS. These give surfactant and co-surfactant (Smix) ratios, i.e., 1:1 & 2:1.

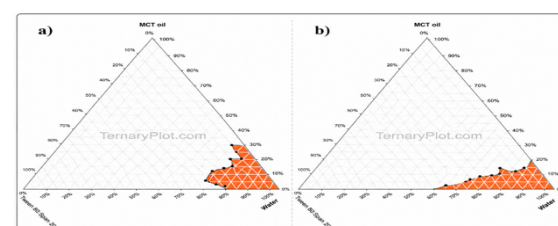


Figure 4. Pseudo Ternary Phase Diagram of Smix Ratio: a) 2:1 b) 1:1

Evaluation of L-SEDDS

Viscosity

During the viscosity study, it was noticed that the surfactant & co-surfactant concentration increased the viscosity of the formulation. The viscosity of the formulation ranged from 132 to 155 mPa.s.

Emulsification Time

An emulsification time study was performed for each batch it shows the time taken by L-SEDDS to form the emulsion. The time ranged between 34 and 70 seconds.

Drug Content

Drug content of L-SEDDS was determined to be 65.61 to 98.67 % that indicates the drug loading capacity.

In vitro Dissolution Study:

In vitro dissolution studies of Lutein L-SEDDS showed a progressive rise in cumulative drug release with time. A dissolution profile of Lutein optimized L-SEDDS (F5) showed the rapid release of the drug in pH 6.8 phosphate buffer, which was $98.89 \pm 0.02\%$ within 30 minutes. F1 & F2 showed the lowest drug release, $79.41 \pm 0.06\%$ and $80.01 \pm 0.54\%$ at 30 min. F3 batch showed rapid release at the start and reached $84.55 \pm 0.88\%$. F4, F6, F7, F8 and F9 exhibited improved release profile with $94.58 \pm 0.87\%$, $92.40 \pm 0.86\%$, $90.32 \pm 0.46\%$, $89.97 \pm 1.04\%$ and $96.07 \pm 1.30\%$ release in figure no. 5 respectively.

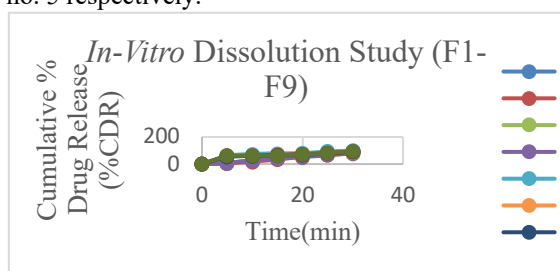


Figure 5. *In vitro* Dissolution Study of F1-F9 (L-SEDDS)

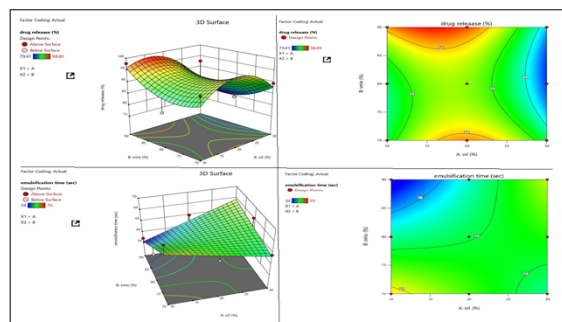


Figure 6. 3DSurface and Contour Plot Graph for % Drug Release and Emulsification Time. Drug release decreased with higher oil content and increased with rising Smix concentration. Maximum drug release (98.89%) was demonstrated by the optimized formulation at low oil and high Smix levels. ANOVA verified that the decreased cubic model had a statistically significant impact on drug release ($F = 16.30$, $p = 0.0220$). As the concentration of Smix increased and the oil content fell, the emulsification time decreased. At low oil and high Smix levels, the optimized formulation had the fastest emulsification time (34 s). ANOVA verified that the decreased quadratic model had a statistically significant impact on emulsification time ($F = 9.40$, $p = 0.0142$). These results show that the SEDDS formulation's ability to self-emulsify is improved by higher Smix and lower oil concentrations. Numerical optimization

identified an optimal formulation using 20.627% oil and 81.706% Smix (desirability = 0.912), predicting 98.476% drug release and 30.893 s emulsification time. As the F5 formulation closely matched these optimized conditions, it was selected as the optimized batch.

Emulsion Grade

The optimized L-SEDDS quickly produced a homogeneous yellow-orange emulsion in 34 seconds after being diluted with distilled water^{32,33}. After emulsification, there was no discernible phase separation, demonstrating the emulsion's strong physical stability.

Droplet size, PDI, and Zeta potential

These tests are performed for the optimized batch only. With the help of an Anton Paar Litesizer DLS 500 using the dynamic light scattering method, droplet size was obtained. The obtained zeta potential value indicates that the developed L-SEDDS formulation has good stability and can maintain a stable dispersed system.

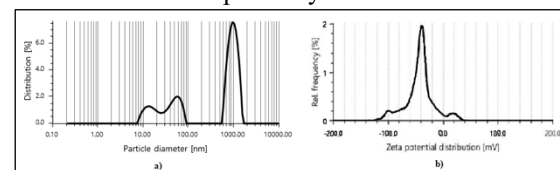


Figure 7. a) Droplet Size, b) Zeta Potential Distribution

Stability

The results determined from stability data were discovered to be satisfactory after a period of 2-month at temperature $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\%$.

Table 4. Stability Study of Optimized Formulation

Formulation	Time of Sampling			
	0 days	15 days	30 days	60 days
Emulsification Time	34 sec	36 sec	37 sec	38 sec
% Drug Release	98.89 ± 0.02	98.80 ± 0.05	97.56 ± 0.10	97.43 ± 0.15

Evaluation for S-SEDDS

Micrometric Properties

Table 5. Flow Properties of Powder (S-SEDDS)

Sr. No.	Formulation Code	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility Index (%)	Angle of Repose
1	S-SEDDS	0.5	0.66	1.32 (good)	24.24 (good)	33.69 (good)

Emulsification Time and *In vitro* Dissolution Study:

The S-SEDDS preparation showed $88.60 \pm 0.14\%$ drug release at 30 minutes, indicating satisfactory dissolution behavior. The percentage drug release increased consistently with time throughout the study. It showed the 70 sec emulsification time.

CONCLUSION

The lutein-loaded L-SEDDS was successfully formulated and optimized using a 3^2 factorial design. The optimized formulation F5, which contained 80% Smix and 20% MCT oil, showed improved drug release ($98.89 \pm 0.02\%$ within 30 min), high drug content (98.67%), and quick self-emulsification (34 s). The substantial impact of formulation factors on drug release and emulsification time was validated by DOE analysis. The optimized formulation demonstrated acceptable stability under accelerated conditions, as well as acceptable droplet size (462.8 nm), PDI (0.379), and zeta potential (-39.4 mV). The new system's potential for enhancing lutein dissolution and promoting the making of solid dosage forms was demonstrated by the successful conversion of optimized L-SEDDS into S-SEDDS.

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