

Formulation Development and Evaluation of Self-nanoemulsifying Drug Delivery System of Vitamin A for Better Bioavailability

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Abstract

Aims: The objective of the investigation is to formulate self-nanoemulsifying drug delivery system (SNEDDS) of Vitamin A (tocopherol) to improve its aqueous solubility as its fat-soluble vitamin. **Settings, Design, Methodology:** Solubility of Vitamin A in various oil surfactants and cosurfactants is determined. Ternary phase diagram is constructed at different ratios of surfactant and co-surfactants to determine self-emulsifying region. Effect of oil content, pH of aqueous phase and mean globule size of resulting nano-emulsion is studied. Optimized formulation was identified and was evaluated for *in vitro* dissolution profile in comparison with pure drug. **Results:** Self-emulsifying drug delivery systems yielded nanoemulsion with globule size range of 81.7 nm with the Z average of 504.4 nm indicating all the particles were in nano-meter range. Drug content was measured and found to be 99.62% in optimized formulation A20. Phase inversion is not noticed after thermodynamic studies. **Conclusion:** SNEDDS of Vitamin A comprising of clove oil, Tween 40, and polyethylene glycol 600 were prepared for enhancing the dissolution and bioavailability. SNEDDS were optimized based on the optimum globule size, increased dissolution, and drug release. Close to complete drug release was achieved from the formulation A20 which is significantly higher as compared to that of other formulations.

Key words: Improving aqueous solubility, self-nanoemulsifying drug delivery system, Vitamin A

INTRODUCTION

Approximately 40% of new drug candidates have poor water solubility, and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and intersubject variability, and a lack of dose proportionality.^[1] To overcome these problems, various formulation strategies are exploited. Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs.^[2,3] SEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents, and cosolvents/surfactants.^[4] On mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions

or microemulsions (self-microemulsifying drug delivery systems [SMEDDS]). Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water.^[5,6]

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METHODOLOGY

Solubility studies

Solubility of Vitamin A in various oils was determined using shake-flask method of determining solubility; in this method, excess of drug was added to vials containing 1 ml of excipients and was vortexed for 10 min and then shaken for 48 h at 25°C, and visual inspection is done after 48 h.^[7]

Emulsification studies

From the large pool of surfactants, surfactant with best self-emulsifying abilities was selected. The selected oil and surfactant were mixed in 1:3 ratio and heated up to 40–45°C and then vortexed to form homogeneous mixture. The ratio of oil to surfactant was decided on the basis of requirement by Pouton. Various cosurfactants were screened by mixing surfactants with cosurfactants in 2:1 ratio; oily phase was added to this mixture in 1:3 ratio, and then, they were heated and vortexed gently to form a homogeneous mixture and were evaluated visually.^[8]

Construction of pseudoternary phase diagram

Pseudoternary phase diagram of oil, surfactant, cosurfactant, and water was developed using titration method at 25 ± 2°C; phase behavior system was studied at 1:1, 2:1, 3:1, and 4:1 ratios of surfactant and cosurfactant, and the resulting mixture was evaluated visually for transparency. The endpoint of titration where mixture becomes turbid or phase separation was observed at this point; amount of water surfactant and cosurfactant used is noted.^[7]

Preparation of Vitamin A self-nanoemulsifying drug delivery system (SNEDDS)

Vitamin A self-emulsifying system was prepared by dissolving drug in cosurfactant in a transparent glass vial; then, calculated quantities of surfactant and oil were transferred into the above vial, and components in vial were mixed thoroughly and heated at 40–50°C to form homogeneous mixture and were stored at room temperature until used.

Globule size analysis

The mean globule size was analyzed using Zetasizer with the following parameters:^[9]

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Measurement Results	
Date	Tuesday, June 11, 2019 12:10:47 PM
Measurement Type	Particle Size
Sample Name	LID 1
Scattering Angle	90
Temperature of the Holder	24.9 °C
Dispersion Medium Viscosity	0.897 mPa·s
Transmission Intensity before Meas.	10599
Distribution Form	Standard
Distribution Form(Dispersity)	Monodisperse
Representation of Result	Scattering Light Intensity
Count Rate	4395 kCPS

Stability studies

Thermodynamic stability studies of optimized formulation of Vitamin A SNEDDS were assessed as per the ICH guidelines.

RESULTS AND DISCUSSION

Solubility studies

Preliminary solubility analysis was carried out to select the appropriate excipient from various oils such as clove oil, cotton seed oil, olive oil, castor oil, eucalyptus oil, emu oil, sesame oil, and oleic acid; surfactants such as Tween 40, Tween 80, Span 60, and Span 80; and cosurfactants such as polyethylene glycol (PEG) 600. Based on drug solubility, clove oil was used as oil phase and Tween 40 and PEG 600 were used as surfactant and cosurfactant, respectively [Figures 1-3].

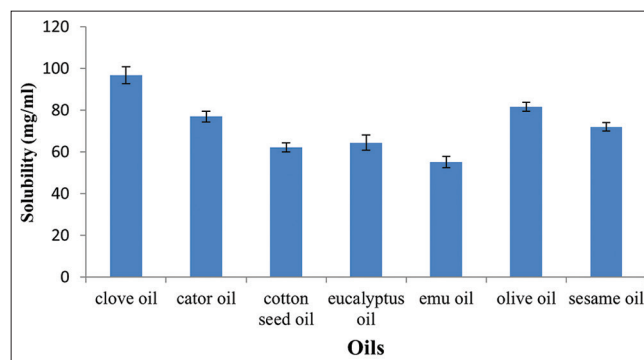


Figure 1: Solubility studies of Vitamin A in oil

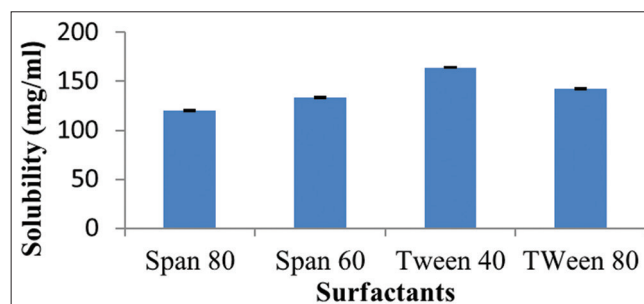


Figure 2: Solubility studies of Vitamin A in surfactants

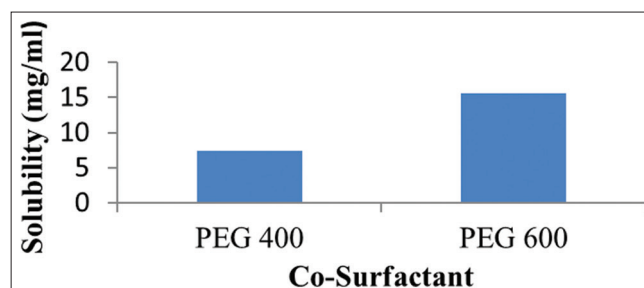


Figure 3: Solubility studies of Vitamin A in cosurfactants

Pseudoternary phase diagram

From the solubility studies, clove oil, Tween 40 and PEG 600 were selected as oil, surfactant and co-surfactant respectively. From the phase diagram [Figure 4] it was observed that self-emulsifying region was enhanced with increasing concentrations of surfactant and cosurfactant with oil. The efficiency of self-emulsification was good when the surfactant concentration increased.^[10,11]

Visual observation

With the use of visual observation method, the tendency of formation of emulsion was observed. Visual observation test

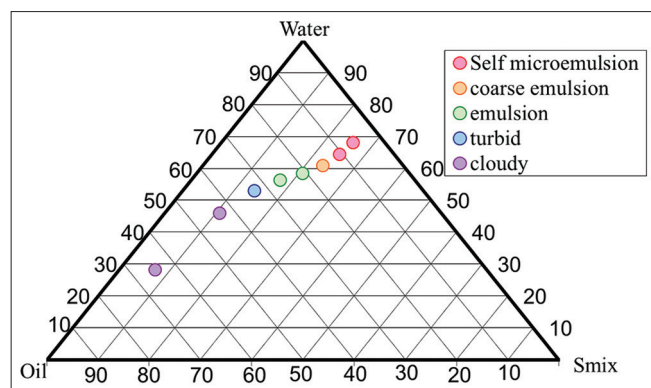


Figure 4: Ternary phase diagram of clove oil, Tween 40, and polyethylene glycol 600 (F20)

was performed for different ratios by keeping the surfactant and cosurfactant ratio (Smix) as 1:1, 2:1, 3:1, and 4:1. Grades were given to the ratios based on the tendency of formation of microemulsion. The ratios 1:9, 2:8, 3:7, and 4:6 of Smix 1:1 and 1:9, 2:8, 3:7, 4:6, and 5:5 of Smix 2:1 and 1:9, 2:8, 3:7, 4:6, 5:5, and 6:4 of Smix 3:1 and 1:9, 2:8, 3:7, 4:6, 5:5, and 6:4 of Smix 4:1 showed rapid formation of microemulsion within a minute having a clear appearance. Therefore, these ratios were selected for the formulation of SNEDDS [Table 1 and Figures 5 and 6].

Thermodynamic stability studies

No phase separation and effect of temperature variations on prepared formulations were observed during thermodynamic stability studies. There was no change in the visual description of samples after centrifugation freeze–thaw cycles. Formulations which are thermodynamically stable only were selected for further characterization.

% Transmittance (%T) measurement

The clarity of microemulsion was checked by transparency, measured in terms of %T. SNEDDS forms o/w microemulsion since water is external phase formulation (A20), which has %T value >99%. These results indicate the high clarity of microemulsion. In case of other systems, %T values were <99%, suggesting less clarity of microemulsion. This may

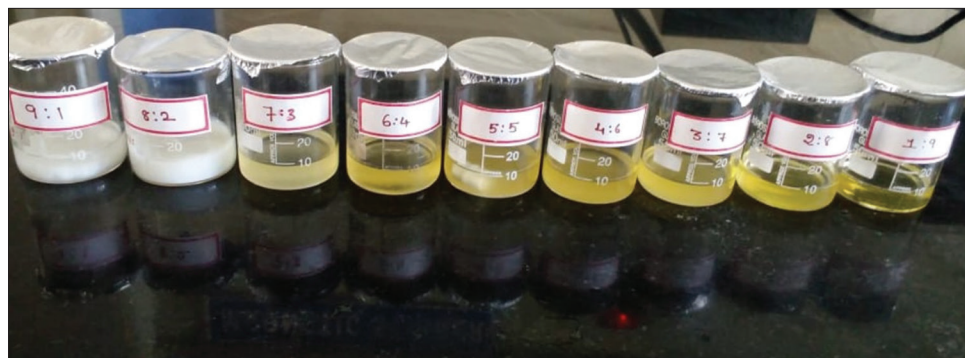


Figure 5: Visual observation test of optimized formulation (F20)

Table 1: Visual observation test for Smix (surfactant: Cosurfactant)

Smix (surfactant: Cosurfactant) ratio 1:1			Smix (surfactant: Cosurfactant) ratio 2:1			Smix (surfactant: Cosurfactant) ratio 3:1			Smix (surfactant: Cosurfactant) ratio 4:1		
O: S mix	Time of self-emulsion (min)	Grade	O: S mix	Time of self-emulsion (min)	Grade	O: S mix	Time of self-emulsion (min)	Grade	O: S mix	Time of self-emulsion (min)	Grade
1:9	<1	I	1:9	<1	I	1:9	<1	I/II	1:9	<1	I/II
2:8	<1	I	2:8	<1	I	2:8	<1	I/II	2:8	<1	I/II
3:7	<1	I/II	3:7	<2	I/II	3:7	<1	I	3:7	<1	I
4:6	<1	I	4:6	<2	III	4:6	<1	I	4:6	<1	I
5:5	<1	I/II	5:5	<2	III	5:5	<2	III	5:5	<2	III
6:4	<1	I	6:4	<2	III	6:4	<2	III	6:4	<2	III
7:3	<2	III	7:3	<2	III	7:3	<1	I	7:3	<1	I

be due to a greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T [Table 2].

Drug content of SMNDDS

Maximum % drug content was found to be 99.62% which was found in the formulation A20 [Table 2].

In-vitro dissolution studies of SNEDDS

The faster dissolution from SNEDDS may be attributed to the fact that in this formulation, the drug is a solubilized

form and on exposure to dissolution medium results in small droplet that can dissolve rapidly in the dissolution medium. The release from liquid SNEDDS formulation (A20) was faster and higher than other SNEDDS formulations indicating influence of droplet size on the rate of drug dissolution [Figures 6-9].

Particle size analysis of SNEDDS

Droplet size determines the rate and extent of drug release as well as drug absorption. Smaller the particle size, larger the interfacial surface area which may lead to more rapid absorption and improved bioavailability. SNEDDS with a mean droplet size below 200 nm exhibit excellent bioavailability. The particle size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate

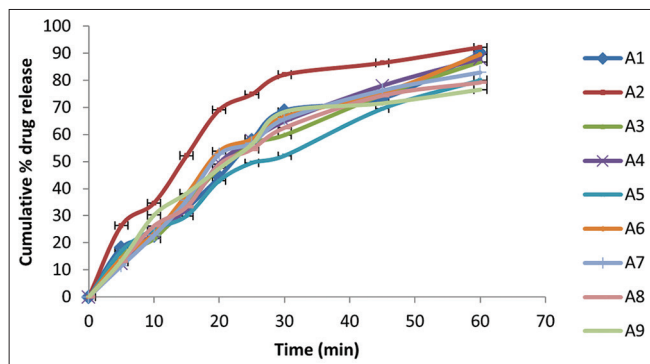


Figure 6: Dissolution profiles of Vitamin A formulations (A1–A9)

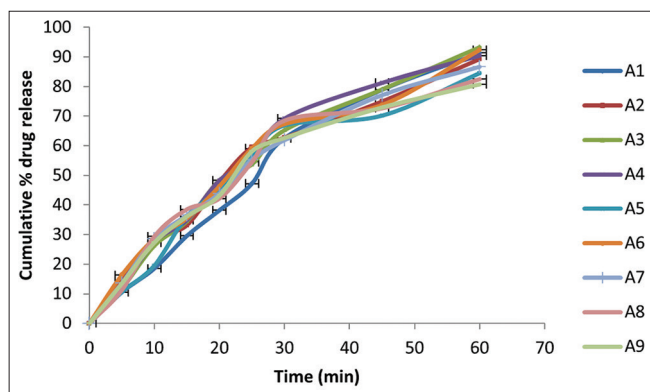


Figure 7: Dissolution profiles of Vitamin A formulations (A10–A18)

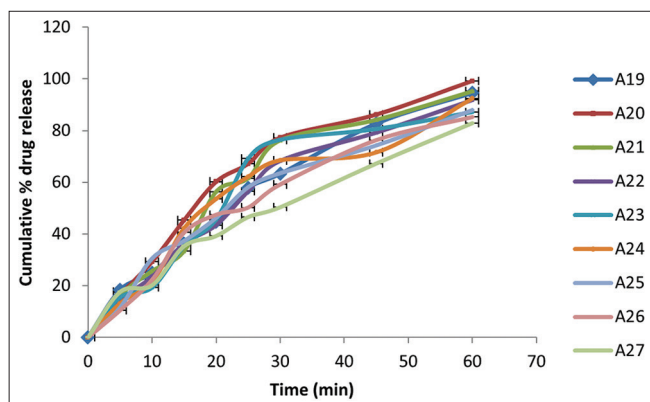


Figure 8: Dissolution profiles of Vitamin A formulations (A19–A27)

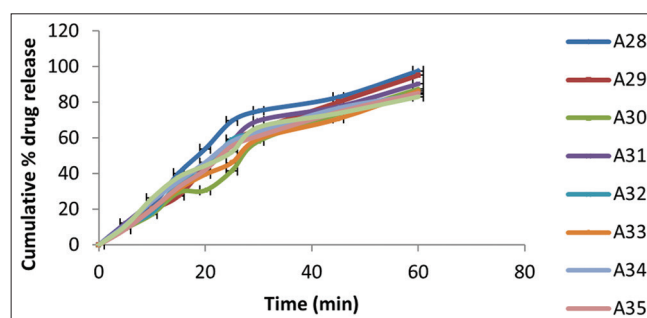


Figure 9: Dissolution profiles of Vitamin A formulations (A28–A36)

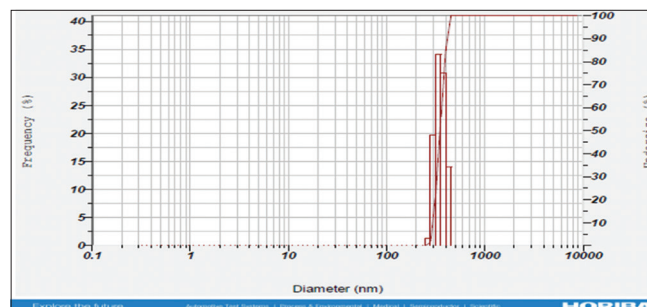


Figure 10: Particle size analysis of optimized formulation A20

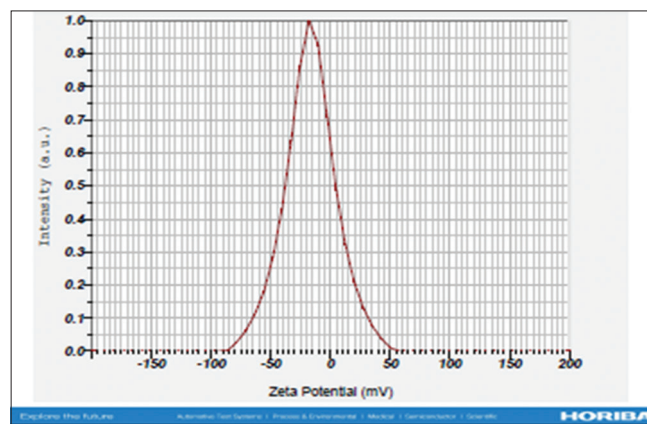


Figure 11: Zeta potential of the optimized formulation A20

Table 2: Visual observation, % transmittance, and % drug content of different formulations

Code	Visual observation	Transmittance	% Drug content	Code	Visual observation	Transmittance	% Drug content
A1	Transparent	90.22	92.56	A19	Transparent	96.25	98.09
A2	Transparent	88.14	91.47	A20	Transparent	99.20	99.62
A3	Slightly clear	86.33	88.29	A21	Transparent	96.33	90.21
A4	Transparent	80.27	86.21	A22	Slightly clear	93.57	92.22
A5	Slightly clear	80.14	87.22	A23	Transparent	91.43	93.74
A6	Turbid	82.19	80.11	A24	Turbid	85.36	93.45
A7	Slightly clear	84.18	79.54	A25	Slightly clear	74.39	82.51
A8	Turbid	62.43	81.55	A26	Slightly clear	81.23	79.26
A9	Turbid	72.82	86.21	A27	Turbid	77.21	72.18
A10	Transparent	91.38	93.96	A28	Transparent	96.24	97.52
A11	Transparent	91.12	95.28	A29	Transparent	94.22	97.39
A12	Transparent	89.25	91.35	A30	Transparent	90.85	93.46
A13	Slightly clear	85.47	88.37	A31	Slightly clear	91.28	92.84
A14	Transparent	88.95	89.36	A32	Transparent	92.33	94.81
A15	Turbid	78.20	86.21	A33	Slightly clear	89.27	90.56
A16	Slightly clear	83.21	83.22	A34	Slightly clear	91.20	92.91
A17	Slightly clear	94.28	91.24	A35	Turbid	80.25	82.03
A18	Turbid	80.31	79.55	A36	Slightly clear	85.69	90.21

and extent of drug release as well as absorption. The particle size of the optimized SNEDDS formulation (A20) was found to be 81.7 nm and Z-average of 504.4 nm, indicating all the particles were in the nanometer range [Figure 10].

Zeta potential of SNEDDS

Zeta potential is responsible for the degree of repulsion between adjacent, similarly charged, dispersed droplets. A zeta potential value of ± 30 mV is sufficient for the stability of a microemulsion. The zeta potential of the optimized SNEDDS formulation (A20) was found to be -16.7 mV which complies with the requirement of the zeta potential for stability [Figure 11].^[12,13]

CONCLUSION

SNEDDS of Vitamin A comprising of clove oil, Tween 40, and PEG 600 were prepared for enhancing the dissolution and bioavailability. SNEDDS were optimized based on the optimum globule size, increased dissolution, and drug release. Close to complete drug release was achieved from the formulation A20 which is significantly higher as compared to that of other formulations.

REFERENCES

- Bo T, Gang C, Jian G, Cai X. Development of solid self-emulsifying drug delivery systems: Preparation techniques and dosage forms. *Drug Discov Today* 2008;13:606-10.
- Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. *Adv Drug Deliv Rev* 2008;60:734-46.
- Murdandea SB, Gumkowskia MJ. Development of a self-emulsifying formulation that reduces the food effect for torcetrapib. *Int J Pharm* 2008;351:15-22.
- Cuine JF, McEvoy CL, Charman WN, Pouton CW, Edwards GA, Benameur H, *et al.* Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic selfemulsifying formulations to dogs. *J Pharm Sci* 2008;97:993-1010.
- Tang J. Self-emulsifying drug delivery systems: Strategy for improving oral delivery of poorly soluble drugs. *Cur Drug Ther* 2007;2:85-93.
- Attama AA, Mpamaugo VE. Pharmacodynamics of piroxicam from self-emulsifying lipospheres formulated with homolipids extracted from *Capra hircus*. *Drug Deliv* 2006;13:133-7.
- Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci* 2006;29:278-87.
- Verreck G, Brewster ME. Melt extrusion-based dosage forms: Excipients and processing conditions for pharmaceutical formulations. *Bull Tech Gattefosse* 2004;97:85-95.
- Groves MJ, Mustafa RM. Measurement of the spontaneity of self-emulsifiable oils. *J Pharm Pharmacol*

- 2004;26:671-88.
10. Ito Y, Kusawake T, Ishida M, Tawa R, Shibata N, Takada K, *et al.* Oral solid gentamicin preparation using emulsifier and adsorbent. *J Control Release* 2005;105:23-31.
 11. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomed Pharmacother* 2004;58:173-82.
 12. Porter CJ, Charman WN. *In vitro* assessment of oral lipid based formulations. *Adv Drug Deliv Rev* 2001;50 Suppl 1:S127-47.
 13. Sek L, Porter CJ, Charman WN. Characterisation and quantification of medium chain and long chain triglycerides and their *in vitro* digestion products, by HPTLC coupled with *in situ* densitometric analysis. *J Pharm Biomed Anal* 2001;25:651-61.

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